KANDIDÁTUSI ÉRTEKEZÉS

MOLDVAI ISTVÁN

1994

KANDIDÁTUSI ÉRTEKEZÉS

EBURNÁNVÁZAS ALKALOIDOK ÉS SZÁRMAZÉKAIK ELŐÁLLÍTÁSA

MOLDVAI ISTVÁN

MAGYAR TUDOMÁNYOS AKADÉMIA
KÖZPONTI KÉMIAI KUTATÓ INTÉZETE

Budapest
1994.

TARTALOMJEGYZÉK

AZ EREDMÉNYEK TÉZISSZERŰ ÖSSZEFOGLALÁSA

ELŐZMÉNYEK ÉS CÉLKITŰZÉSEK

Az átlagos életkor meghosszabodásával a terápiában egyre fontosabb szerepet kapnak azok a gyógyszerek, s a klinikai kutatásban azok a gyógyszerjelöltek, melyek sikerrel alkalmazhatók az öregedés élettani folyamatát kisérő agyi vérellátási elégtelenségek s az ezzel összefüggő memóriazavarok gyógyításában. Ezen tünetcsoport kezeléséhez szükséges antidemenciás hatással mintegy félszáz vegyület rendelkezik, melyek körülbelül tucatnyi alapszerkezetre vezethetők vissza. E vegyületek között több alkaloid is található. Ezek egyike a vinkamin, melynek módosított származékát, a (+)-apovinkaminsav-etilészert az agyi vérellátás illetve az agy oxigén felhasználásának javításában alkalmazzák. A Budapesti Műszaki Egyetem és a Kőbányai Gyógyszerárugyár összefogásával kifejlesztett hazai terméket a Gyár Cavinton márkanévvel forgalmazza. A termék születése széleskörű kutatásokat indított el további, még kedvezőbb élettani hatású molekulák előállítására, valamint a kémiai szerkezet — biológiai hatás összefüggésének tanulmányozására.

E munkában Intézetünk, az MTA Központi Kémiai Kutató Intézete is bekapcsolódott. Szántay Csaba akadémikus vezetésével 1977-ben a "Természetes Szerves Anyagok Szintézise " osztályon is megindult az indolvázas alkaloidok, s a későbbiekben ezzel szoros összefüggésben az antidemenciás hatásúnak remélt vegyületek kutatása. Az Osztály ilyen irányú munkájában 1982 óta veszek részt; kezdetben mint a Kőbányai Gyógyszerárugyár kutatója, majd 1987-től mint az Intézet tudományos munkatársa.

Ez a disszertáció erről az évtizednyi kutatómunkáról kíván számot adni azon eredmények bemutatásával, melyek az eburnánvázas alkaloidokra vonatkoznak, s melyek tudományos közlemények illetve szabadalmak formájában nyilvánossá válhattak. A disszertáció 4 főfejezetben 9 témakört ismertet, melyek mindegyike szoros együttműködés eredményeként jött létre egyrészt a "műszeres", másrészt a farmakológus kollégákkal.

Az eredmények bemutatásánál vezérfonalként igyekeztem többé-kevésbé kronológiai sorrendet követni.

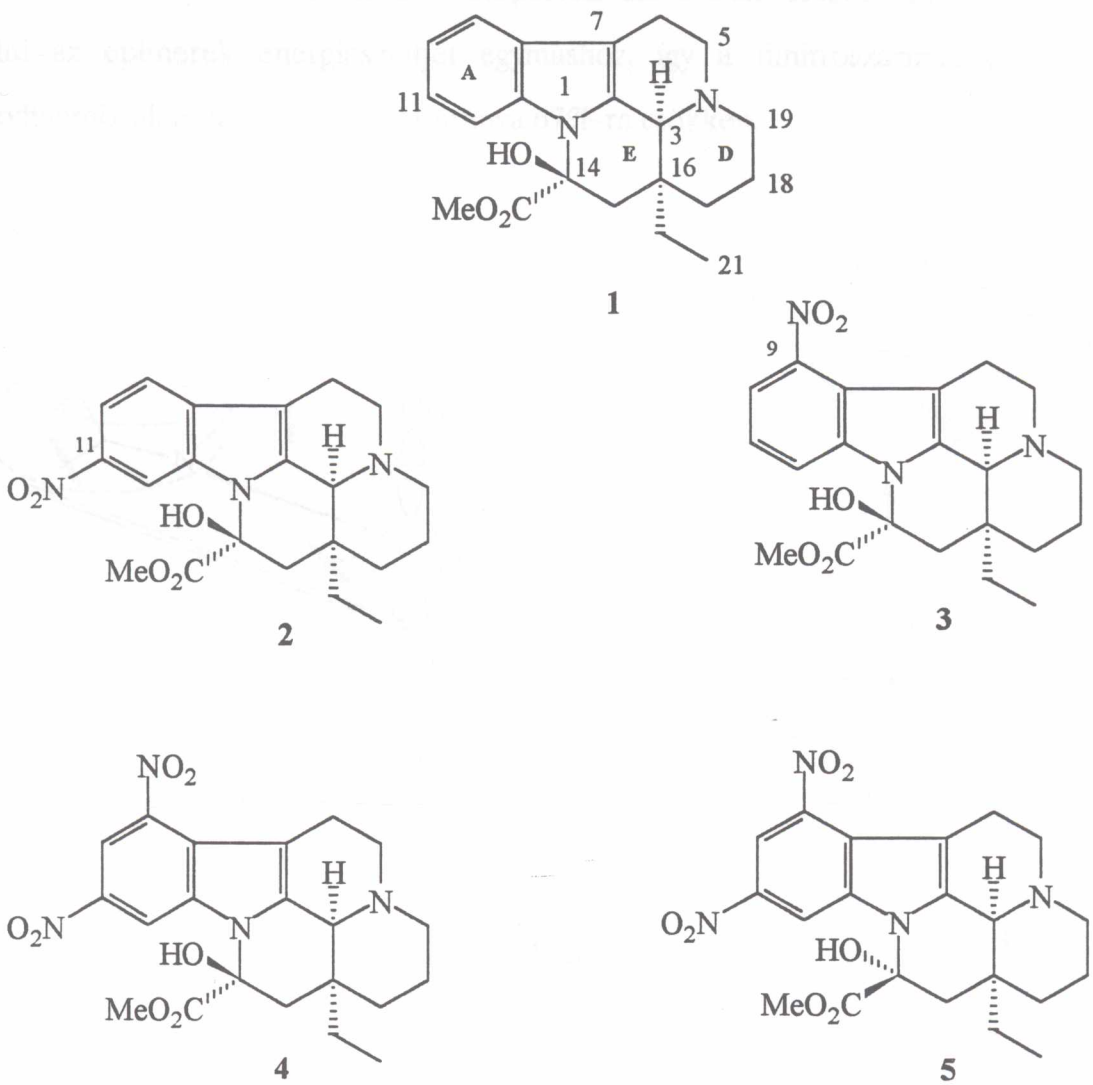
ÚJ TUDOMÁNYOS EREDMÉNYEK

A-gyűrűben szubsztituált vinkamin származékok

1.) Aromás szubsztituenseffektus a C14-epimerizációban [8]

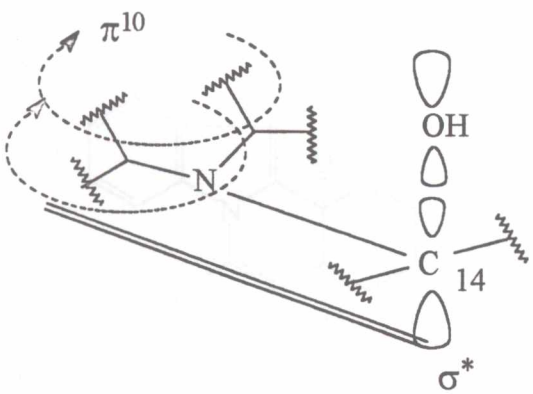
A vinkamin (**1**, 1. ábra) nitrálásával az Omnium Chimique S.A. kutatói a 11-nitro-vinkamint (**2**) kapták, míg minor strukturizomerként a 9-nitro-vinkamint (**3**) izolálták.

A nitrálási reakció tanulmányozása során megállapítottuk, hogy a nitrálást 40 °C-on végezve két nitro-csoport is beépül a vinkamin A-gyűrűjébe. A dinitro-származékok (**4**; 48%, **5**: 18%) — a mononitro-származékokkal ellentétben — C14-epimerek elegyeként keletkeznek, s oszlopkromatográfiás módszerrel választhatók el egymástól.

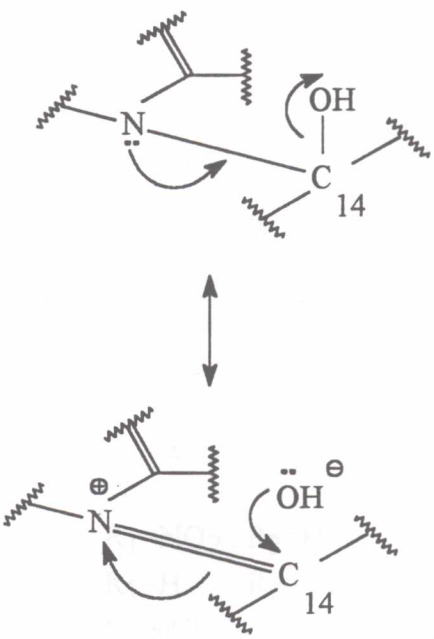


1. ábra

Az **5** C14-epimer keletkezése kapcsán vizsgáltuk meg néhány A-gyűrűn lévő szubsztituens hatását a vinkamin ⟸⟹ C14-epivinkamin egyensúlyra. Megállapítottuk, hogy a fenti egyensúly egyensúlyi állandója függ az A-gyűrűn lévő szubsztituensek elektronikus hatásaitól. A jelenség magyarázataként értelmeztük a vinkamin és C14-epivinkamin származékok stabilitási viszonyait. A vinkamin-származékok stabilabb voltát a kvázi-axiális hidroxil-csoport jelenlétéből adódó anomer-effektushoz hasonló, másodlagos kötőerőnek tulajdonítjuk. Eszerint a hidroxil-csoport C14—O kötésének σ^*-orbitálja szintén részt vesz az indol delokalizált π-elektronrendszerében (2. ábra, A), vagy a rezonancia-elmélet terminológiáját használva: kettős kötést is tartalmazó rezonáns határszerkezetet írhatunk fel (2. ábra, B). Az aromás gyűrűn lévő szubsztituensek hatása a fentiek alapján úgy értelmezhető, hogy az elektronszívó csoportok ezt a másodlagos kötőerőt csökkentve közelíti az epimerek energiaszintjét egymáshoz, így a dinitroszármazék esetében a termodinamikailag stabilabb epimer aránya 67%-ra csökken.



A

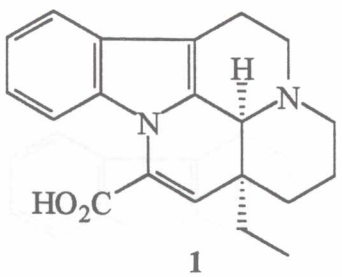


B

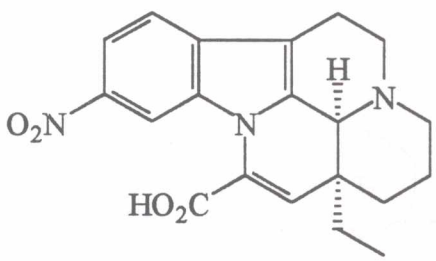
2. ábra

2.) Nitro-apovinkaminsav-származékok: előállítás és biológiai hatások [2, *14*, *15*]

A-gyűrűben nitro-csoportot tartalmazó apovinkaminsav-származékok előállításához nitráltuk az apovinkaminsavat (**1**, 3. ábra). A 11-nitro-apovinkaminsav (**2**) és a 9-nitro-apovinkaminsav (**3**) körülbelül 1 : 1 arányban keletkezik, s frakcionált kristályosítással választhatók szét egymástól. A **2** és **3** vegyületekből nitro-apovinkaminsav-észterekhez különböző módokon (direkt észteresítés, alkilezés alkil-szulfátokkal illetve alkil-halogenidekkel, savklorid készitése utáni alkoholízis) jutottunk.



1



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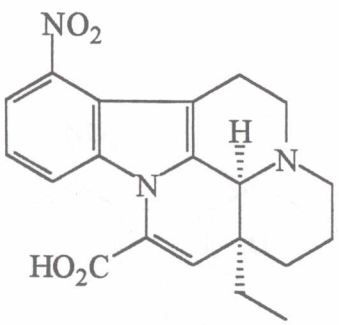

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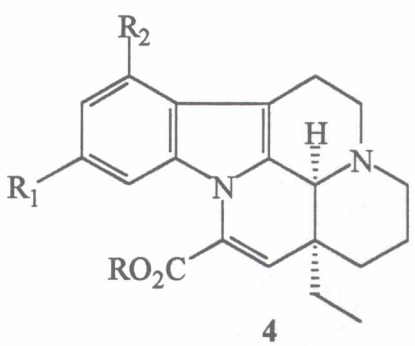


4

R_1=NO_2, R_2=H
R_1=H R_2=NO_2
R =alkil

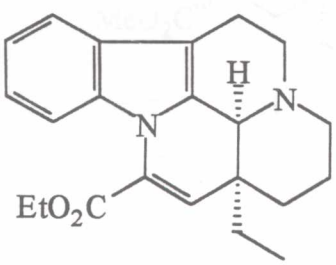
3. ábra

A **4** általános képletű vegyületekből (3. ábra) több tucat származékot állítottunk elő. A biológiai hatások tanulmányozása azt mutatta, hogy a szubsztituált vegyületek növelték a referencia-vegyület (**4**; R=Et, R_1=R_2=H) keringési, görcsgátló és antihipoxiás hatásait.

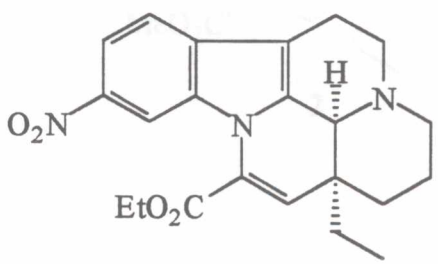
3.) Az apovinkaminsav-etilészter nitrálása során képződő új termék szerkezete [6]

Az apovinkaminsav-etilészter (**1**, 4. ábra) nitrálása során a várt 11- és 9-nitro-származékok (**2**, **3**) mellett minor termékként egy 7,10-dinitro-származék (**4**; 12%) is keletkezett, melynek további szerkezeti különlegessége, hogy az indol-gyűrűrendszer indolinná alakult. A részletes NMR-vizsgálatok alapján a **4** vegyület képlete a 4. ábrán látható, s a vegyület szerkezetét röntgendiffrakciós vizsgálat is alátámasztotta.

Megemlítendő még, hogy hasonló szerkezetű származék a vinkamin nitrálása során nem izolálható.



1



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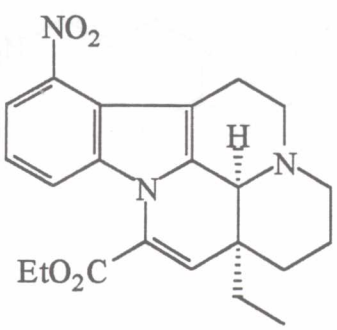

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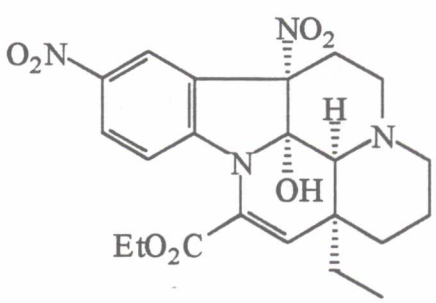


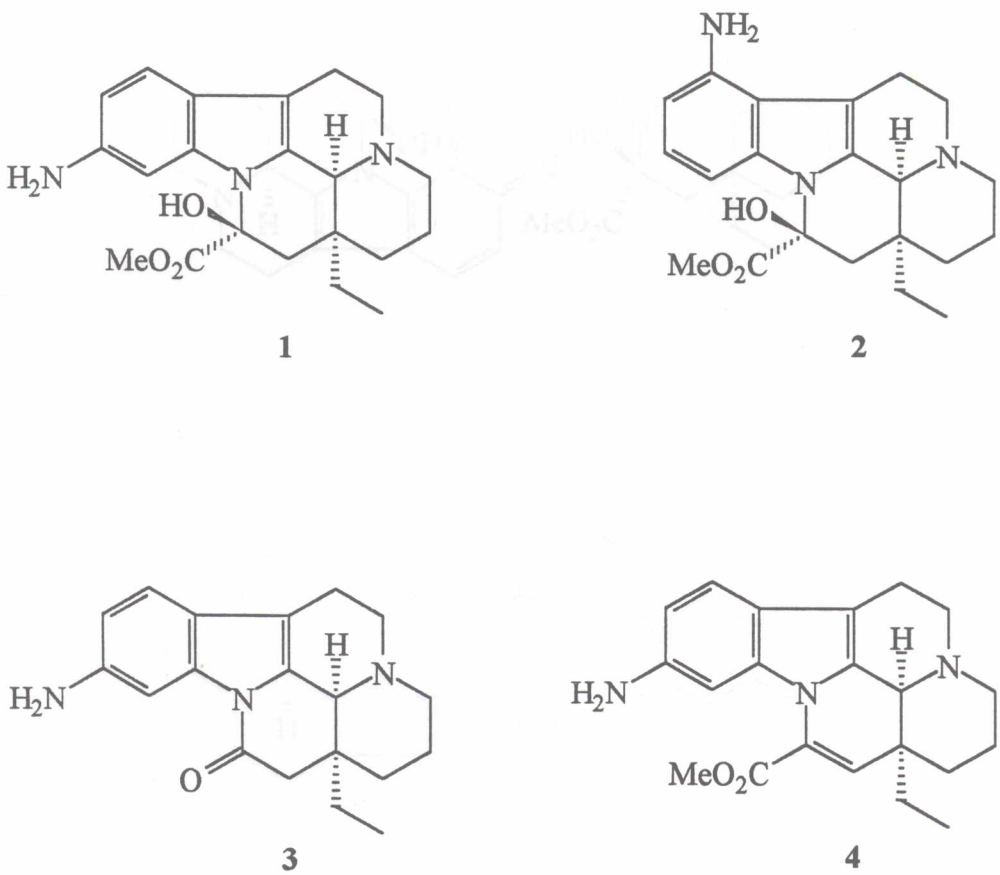
4

4. ábra

Vinca-alkaloidok és származékaik reakciói jóddal

4.) Indol-vegyületek fenazin-származékainak keletkezése [*16, 5, 7*]

Az Omnium Chimique S.A. kutatói a nitro-vegyületek redukciójával számos amin előállítását is leírták (**1-4**, 5. ábra).

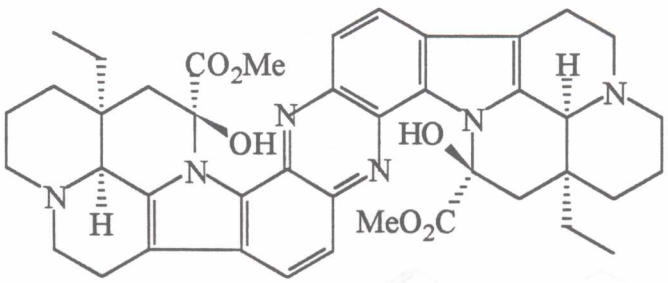


5. ábra

Ezen aminok felhasználásával mintegy félszáz acilamino-származékot állítottunk elő farmakológiai vizsgálatokhoz.

Az aminok egyéb reakcióit vizsgálva azt találtuk, hogy a 11-amino-vinkamin (**1**) és a 11-amino-apovinkamin (**4**) különös módon reagálnak jóddal. Igy például az **1** amint használva kiindulási anyagként a várt diszubsztituált jód-származék helyett dimer fenazin-származék

(**5**, 30%; 6. ábra) képződött. A **4** amin a hasonló szerkezetű **6** dimert szolgáltatta, amely az **5** dimerből víz eliminációjával is előállítható. Fenazinok keletkezését aromás aminok jóddal való reakciójakor ezideig nem írták le az irodalomban. Ugyanakkor a reakció speciális jellegét jelzi, hogy a 9-amino-vinkamint (**2**) használva kiindulási anyagként, izolálható termék nem keletkezett. Hasonlóképpen nem észleltünk fenazin képződést a **3** amin esetében sem.



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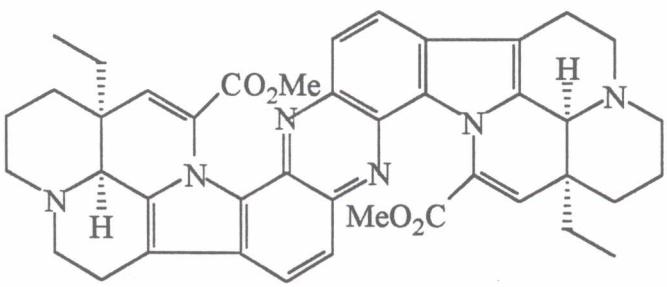


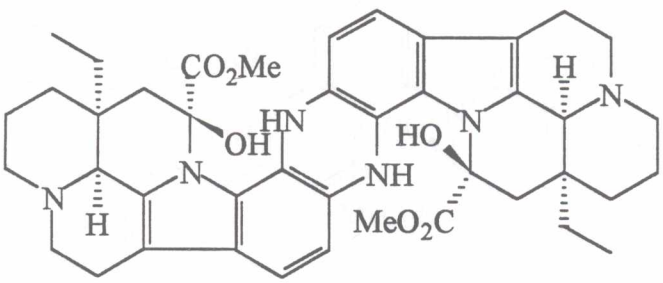
6

6. ábra

Az **5** fenazin dimer előállítását vizsgálva megállapítottuk, hogy egyéb oxidálószerek (például: kálium-permanganát, Fetizon-reagens, mangán-dioxid stb.) is alkalmasak a fenazin-gyűrűrendszer kialakításához.

A fenti kísérleti tények alapján a végtermék képződésére kétféle alternatív magyarázatot

adtunk. Mindkettőben közös az, hogy a fenazin végtermék kialakulását a **7** dihidro-származék aromatizációjaként értelmezi. E vegyület képződhet a diszubsztituált monomer (**8**) intramolekuláris nukleofil szubsztitucióját, vagy a másik értelmezés szerint az **1** aminból oxidációval képződő kinoidális imin kation (**9**) cikloaddicióját (7. ábra). Az utóbbi reakcióutat több fentebb megemlített kísérleti megfigyelés is valószínűsít: részben az, hogy a fenazin-gyűrűrendszer kialakítása különböző típusú oxidálószerekkel is megvalósítható; másrészt érthetővé teszi, hogy **3** amin esetében a savamid-csoport megakadályozza a kinoidális imin kation kialakulását, és ebből adódóan elmarad a dimerizáció is.



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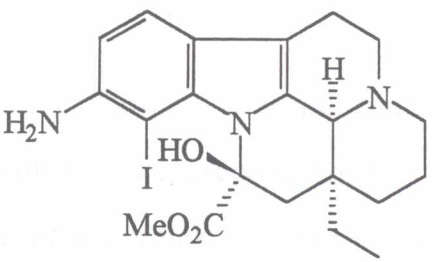

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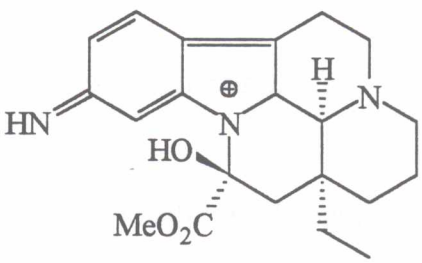
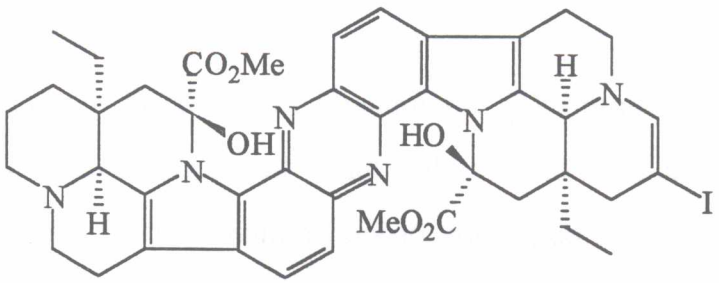


9

7. ábra

Ha az **1** amint nagyobb jód felesleggel reagáltatjuk, mint amennyi a fenazin-származék képzéséhez szükséges, az **5** főtermék mellett olyan melléktermékeket is kaptunk, amelyek

β-jód-enamin szerkezeti részletet, illetve részleteket is tartalmaztak (**10**, **11**, 8. ábra).



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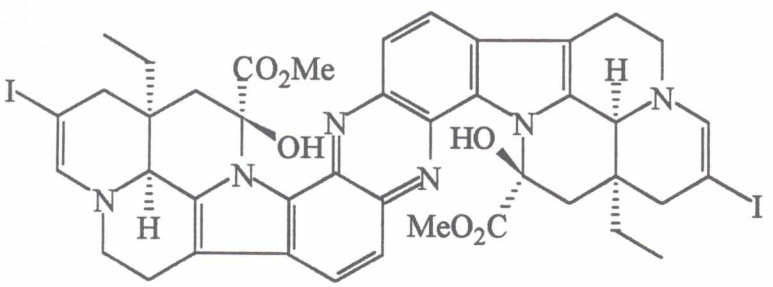


11

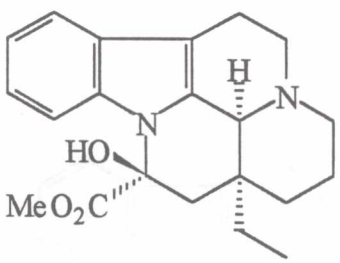
8. ábra

A teljesség kedvéért megemlítendő még, hogy az **5** és **6** fenazinok figyelemreméltó citosztatikus hatással rendelkeznek.

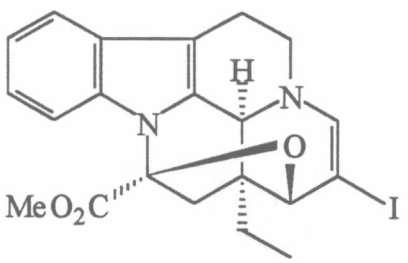
A fenti melléktermékek szerkezeti különlegessége kapcsán kezdtünk el foglalkozni egyéb eburnánvázas vegyületek jóddal való reakciójával.

5.) Kriocerin előállítása vinkaminból [*10, 12*]

A vinkamint (**1**, 9. ábra) kloroform és vizes nátrium-hidrogénkarbonát oldat elegyében szobahőmérsékleten jóddal reagáltatva a 18-jód-kriocerinhez (**2**) juthatunk, melyet korábban LeMen és mtsai a 17,18-dehidro-vinkaminból (**3**) állítottak elő jód + kálium-jodátos oxidációval. Jód alkalmazásával tehát telített vinkamin-származékokból egy lépésben kialakítható mind a β-jód enamin funkció, mind pedig a C14-C17 szénatomok résztvételével egy tetrahidrofuranil-gyűrű.



1



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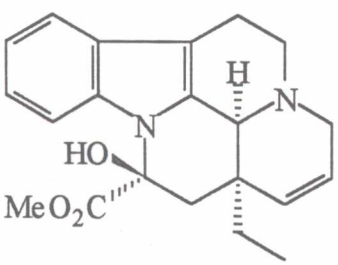

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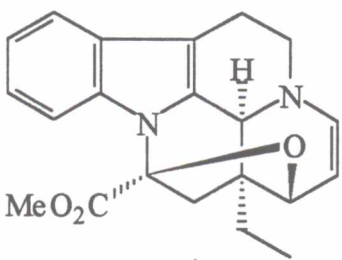


4

9. ábra

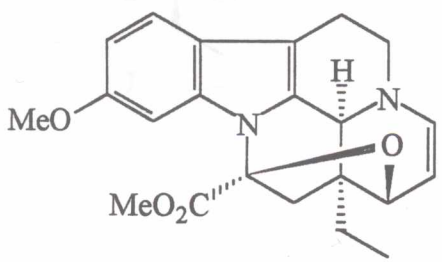
A **2** jód-származék a francia kutatócsoport módszere szerint elvileg savas forralással alakítható át a *Crioceras dipladeniiflorus* alkaloidjává, a kriocerinné (**4**). Saját kisérleteink tanusága szerint azonban ez az átalakítás előnyösen reduktív körülmények között (hangyasavas oldatban csontszenes palládium használata mellett) valósítható meg.

Az, hogy a kriocerin előállításához a nagy mennyiségben is könnyen hozzáférhető vinkamint használtuk kiindulási anyagként, módot nyújtott arra, hogy nagyobb mennyiségben is előállíthassuk ezt a ritka alkaloidot, s így tanulmányozhassuk reakcióit is. Ezek a vizsgálatok jelenleg is folyamatban vannak.

6.) Kraspidospermin előállítása vincinből [*11, 12*]

A kraspidospermin (**1**, 10. ábra) a *Craspidospermum verticillatum* alkaloidja. Félszintézisével több francia kutatócsoport is foglalkozott. Az irodalomban leírt megoldások közös hátránya a viszonylag ritka kiindulási anyag (17,18-dehidro-vincin, **2**) használata.

Az előzőekben ismertetett módszerünkre építve közel kvantitativ termeléssel állítottuk elő a kraspidospermint (**1**) vincinből (**3**) a megfelelő jód-intermedieren (**4**) keresztül.



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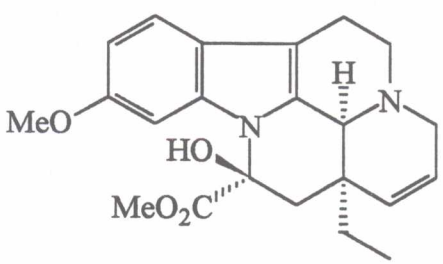

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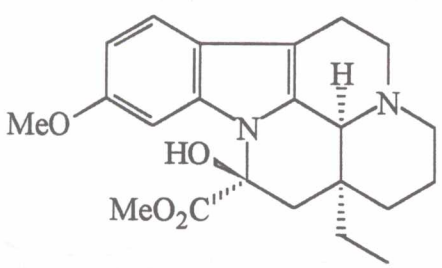

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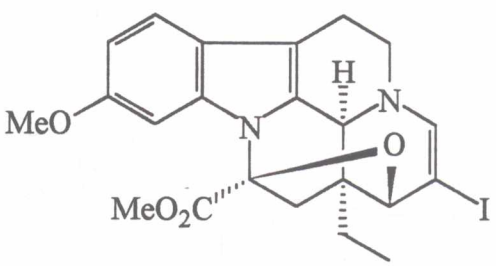


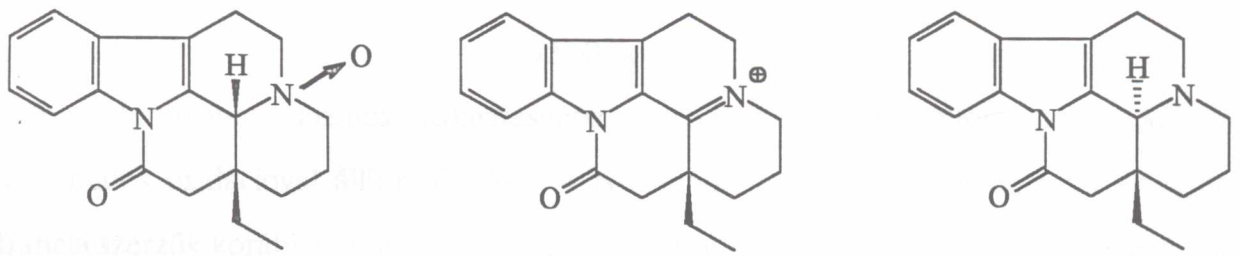
4

10. ábra

A Polonovski-reakció alkalmazása eburnánvázas vegyületek körében

7) Új típusú dimer indol-vegyületek előállítása [*1, 3, 4*]

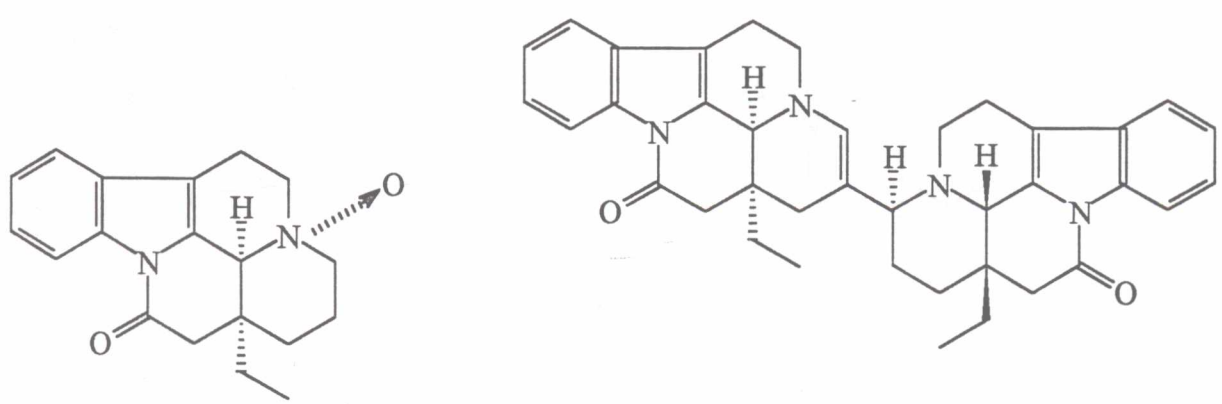
Az Omnium Chimique S.A. kutatói az eburnamonin N-oxidját (**1**, 11. ábra) trifluorecetsav-anhidriddel reagáltatva iminiumsót (**2**), majd ennek redukciójával *transz*-eburnamonint (**3**) kaptak.



1 **2** **3**

11. ábra

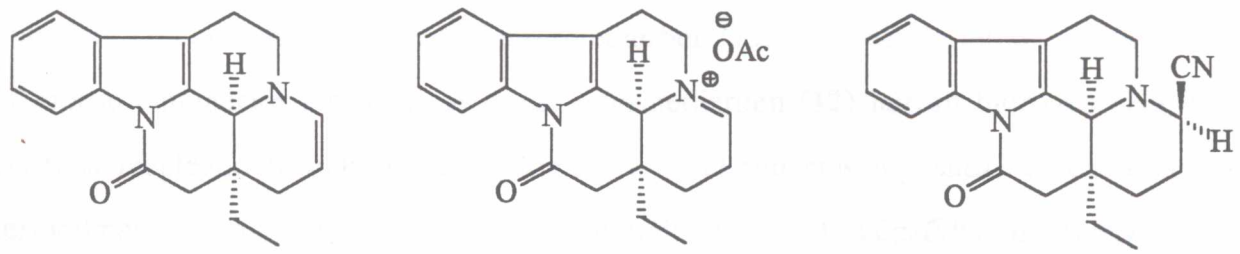
A tükörképi N-oxidot, a vinkamon N-oxidot (**4**, 12. ábra) használva kiindulási anyagként, s elhagyva a redukciós lépést merőben más szerkezetű terméket kaptunk. Az ecetsavanhidrides reakcióelegyből kristályosan kiváló termék egy dimer-vegyület (**5**, 52%). E módszer alkalmazásával több rokonszerkezetű dimert is előállítottunk.



4 **5**

12. ábra

Az **5** dimer kialakulását a reakcióelegyben keletkező enamin (**6**) alkileződéseként értelmezzük a reakciósor bevezető lépésében képződő iminiumsó (**7**) által (13. ábra).

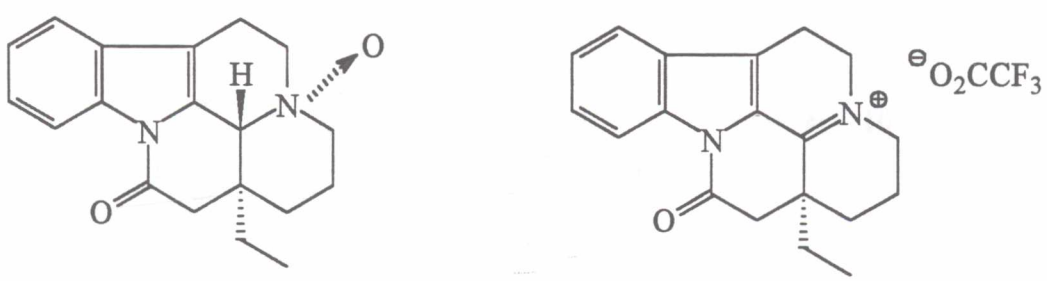


6 **7** **8**

13. ábra

A feltételezett mechanizmus bizonyításához a **6** enamint a fentitől eltérő módon, kálium-dikromátos oxidációval állítottuk elő a **4** N-oxidból. Az izolálható **6** enamin, amelyhez francia szerzők korábban fotokémiai módszerrel jutottak, ecetsav hatására az **5** dimert adta (51%). A dimerizáció másik feltételezett intermedierjét, a **7** iminiumsót, a módosított Polonovski-reakciót követő "cianid-trapping" alkalmazásával α-amino-nitril formájában (**8**, 33 %; 13. ábra) izoláltuk.

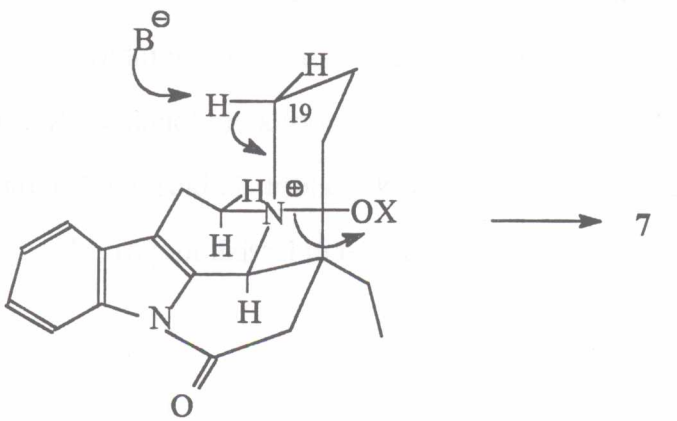
A dimerizáció alkalmazhatóságának határait vizsgálva megállapítottuk, hogy a dimerizáció a C/D *cisz* konformációjú N-oxidokra (pl. **4**) jellemző. A C/D *transz* konformációjú D/E-*transz*-N-oxidok monomer iminiumsót adnak (pl. **9** → **10**, 14. ábra).



9 **10**

14. ábra

E különbséget a sztereoelektronikus faktor figyelembevételével értelmeztük, miszerint a *cisz*-sorozatú vegyületekben az N-aciloxi-csoporthoz képest csak egy *transz*-diaxiális térállású hidrogén található a nitrogénnel szomszédos szénatomokon ($H19_{ax}$), így ez támadható előnyösen a **11** N-aciloxi intermedierben (15. ábra) egy kinetikusan kontrollált E2-tipusú eliminációs lépésben. A *transz* intermedierben (**12**) három hidrogén (H3, H5, H19) is megfelelő térbeli helyzetet foglal el az eliminációs lépéshez, és ezesetben a termodinamikailag legstabilabb, delokalizált iminiumsó (**10**) képződik, minthogy ennek kialakulása igényli a legkisebb energiabefektetést az átmeneti állapotban.



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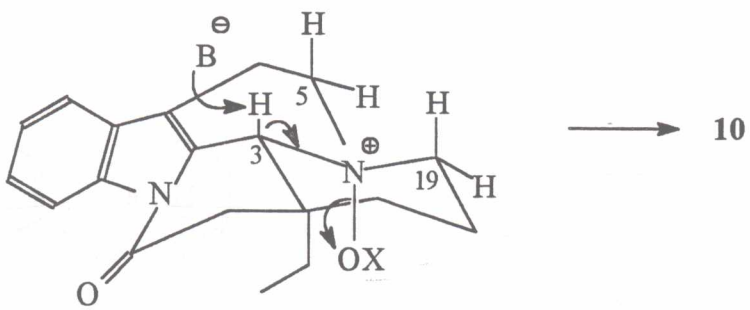


12

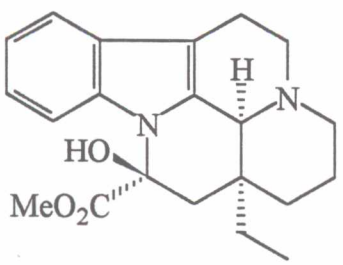
15. ábra

E-gyűrűben módosított Vinca-alkaloidok

8.) Az apovinkamin egyszerű átalakítása vinkaminná [*11, 12*]

A vinkamin (**1**, 16. ábra) illetve a 14-epivinkamin (**2**) apovinkaminná (**3**) való átalakítására több jól használható módszer ismert. Az ellenkező irányú, azaz az apovinkamin vinkaminná történő átalakítására is található néhány példa az irodalomban, de ezek gyakorlati alkalmazhatósága erősen korlátozott.

A fenti átalakítás vizsgálata során azt találtuk, hogy az apovinkamint tömény sósavas oldatban nátrium-nitrit vizes oldatával reagáltatva a hipoklórossav elemei addicionálnak a C14-C15 kettős kötésre. A reakcióban kapott 15α-klór-vinkamin (**4**, 72%) szerkezetét részletes spektroszkópiai módszerekkel, többek között röntgendiffrakciós módszerrel is igazoltuk. A **4** klór-vegyület hidrogenolízissel jó termeléssel (85 %) alakítható vinkaminná.



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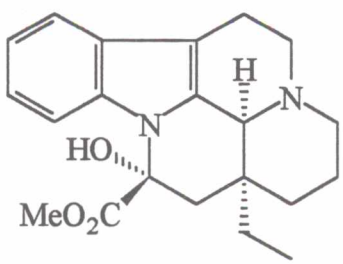

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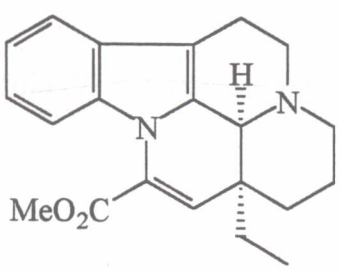

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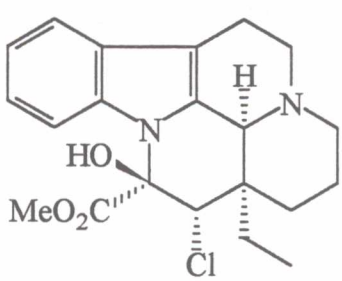
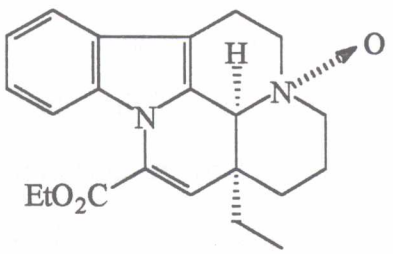


4

16. ábra

15-Klór-származékot más úton is előállítottunk: az **5** N-oxidot (17. ábra) tionil-kloriddal reagáltatva szintén 15α-klór vegyület (**6**, 30%) keletkezik.



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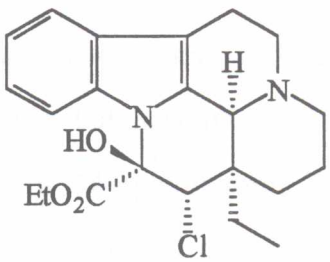

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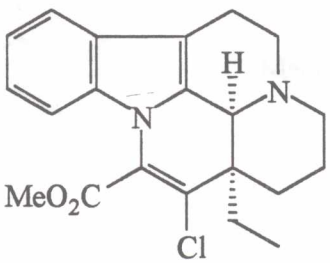


7

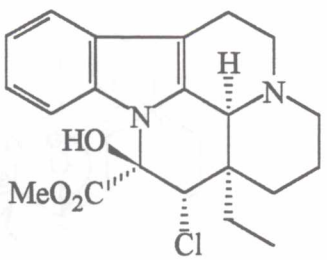
17. ábra

Itt szeretném megemlíteni, hogy mindkét "klórozási" eljárás mechanizmusáról — több elvégzett kísérlet ellenére is — csak találgatásaink vannak. A mélyebb részletek megismerésére jelenleg is folynak vizsgálatok.

A klór-származékok (pl. **4**) savas kezelés hatására könnyen vizet veszítenek a megfelelő 15-klór-apovinkamin (**7**) keletkezése közben.

9.) C15-atomon szubsztituált eburnánvázas vegyületek [*13*]

Az előző pontban ismertetett klór-vegyületek (pl. **1**, 18. ábra) reakcióit vizsgálva azt találtuk, hogy bázisok hatására könnyen epoxidokká (pl.: **2**) alakulnak. A **2** származék epoxid-gyűrűje mind vizes, mind alkoholos oldatban savas katalízis használata mellett könnyen felnyílik. A reakció terméke az első esetben a 14-epivinkamin 15β-hidroxi származéka (**3**, 47%), míg például metanolos oldatban a megfelelő éter-származék (**4**, 42%) keletkezik.



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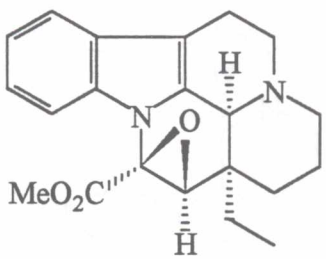

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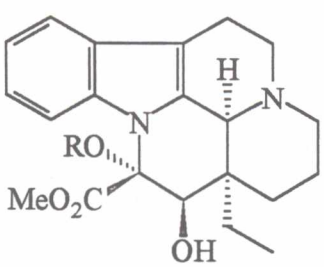
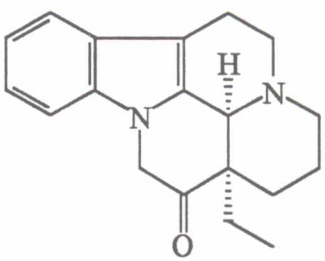


3 R=H

4 R=Me

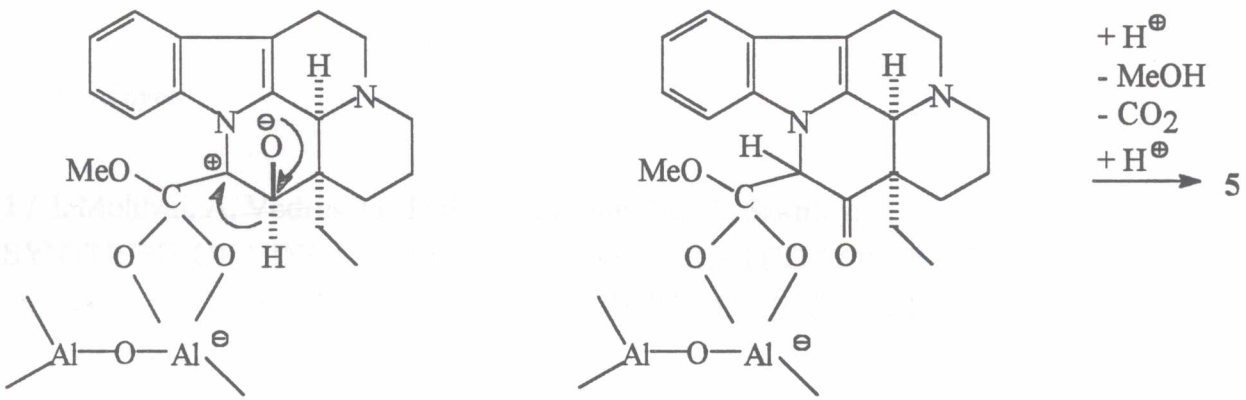


5

18. ábra

Az **1** klór-vegyületből kiindulva 15-fluor-származékot kívántunk előállítani. Míg az **1** klór-származékot különböző típusú oldószerekben kálium-fluoriddal reagáltatva csak a kiindulási anyagot tudtuk kimutatni a reakcióelegyben, addig aluminium-oxidra vitt kálium-

fluoridot használva az **5** ketont izoláltuk (termelés: 83 %). A reakciót részletesebben vizsgálva kimutattuk, hogy ez a keton a **2** epoxidon keresztül keletkezik. A feltételezett mechanizmus szerint a **2** epoxidból és a fluoridion által aktivált aluminium-oxidból képződő **6** ortoészterben (19. ábra) az epoxid-gyűrű felnyílása közben 1,2-hidridanionvándorlás történik. Az így keletkező **7** ortoészter metoxicsoportja a továbbiakban protonálódik, majd metanol és szén-dioxid kilépése után a visszamaradó karbanion protonfelvétellel alakul az **5** ketonná.



6 **7**

19. ábra

Az **5** keton, melyet racém formában egy japán és egy francia kutatócsoport korábban már szintetizált, érdekes kiindulási anyagul szolgált további átalakításokhoz, melyek vizsgálata jelenleg is folyamatban van.

AZ EREDMÉNYEK JELENTŐSÉGE ÉS HASZNOSÍTÁSI LEHETŐSÉGEI

A fent vázolt eredmények gyarapítják ismereteinket az eburnánvázas alkaloidok kémiai viselkedését illetően. Az ismertetett vegyületek közül több értékes gyógyászati hatásokkal rendelkezik vagy kiindulási anyagául szolgál biológiailag aktív anyagok szintéziséhez.

A TÁRGYALT TÉMÁKHOZ KAPCSOLODÓ KÖZLEMÉNYEK, SZABADALMAK ÉS ELŐADÁSOK

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KÖZLEMÉNYEK

Ebben a részben négy főfejezetre osztva tizenegy válogatott közlemény található, melyek a disszertációt alkotják. Az érdeklődő Olvasó figyelmét felhívom azonban még két összefoglaló közleményre [*3*, *12*] is, melyek Szántay Csaba akadémikus Moszkvában (1986) és Karachiban (1992) tartott, nyomtatásban is megjelent előadásainak anyagát tartalmazzák; s melyekben az általam elvégzett tudományos kutatások is szerepelnek. Ezek az összefoglaló közlemények tágabb összefüggésben mutatják be annak az iskolának a munkáját, melynek e disszertáció szerzője is tagja. A két review természetesen nem szerepel a dolgozat keretei között, s értelemszerűen hiányoznak a dolgozat anyagához kapcsolódó szabadalmak másolatai is.

A-GYŰRŰBEN SZUBSZTITUÁLT VINKAMIN SZÁRMAZÉKOK

Acta Chimica Hungarica 128 (1), pp. 109—118 (1991)

SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS, XLIX*

AROMATIC SUBSTITUENT EFFECTS IN THE C-14 EPIMERIZATION

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Received June 1, 1989
Accepted for publication August 17, 1989

Some A-ring substituted vincamine derivatives and their C-14 epimers have been prepared and the aromatic substituent effects on the epimeric equilibrium of these compounds investigated.

We have reported that the (−)-14-epivincamine (**1**) ⇄ (+)-vincamine (**2**) equilibrium can be influenced by metal ions [2], and it was found that **2** is thermodynamically more stable than its C-14 epimer in the natural *cis* series [3].

While investigating structure-bioactivity relationships in the Vinca alkaloid field, the influence of aromatic substituents on the above equilibrium was studied.

Materials

For the preparation of different nitrovincamines (+)-vincamine (**2**) was nitrated [4]. When the separation of the two resultant regioisomers (**3** and **5**) was carried out in an acetone/water mixture instead of methanol [4], the formation of their C-14 epimers could be detected by tlc. Otherwise the epimers were prepared by refluxing the A-ring substituted vincamine derivatives in methanol in the presence of aqueous ammonium hydroxide solution followed by separation using column chromatography (Scheme 1).

At elevated temperature (40 °C) the nitration of (+)-vincamine yielded two major components. After work-up (+)-9,11-dinitrovincamine (**9**) and

* For Part XLVIII, see Ref. [1].
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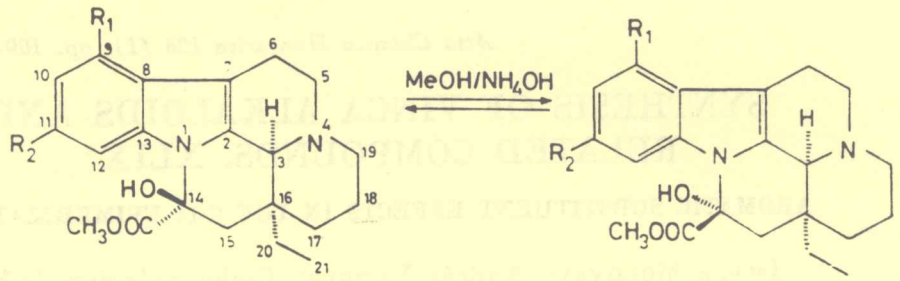


3	R_1 = H	R_2 = NO_2	**4**
5	R_1 = NO_2	R_2 = H	**6**
7	R_1 = H	R_2 = Br	**8**
2	R_1 = H	R_2 = H	**1**

Scheme 1

(−)-9,11-dinitro-14-epivincamine (**10**) were isolated* proving that epimerization had occurred under the given conditions. Both epimers afforded (+)-9,11-dinitroapovincamine (**11**) after elimination of water. Nitration of a mixture of **3** and **5** at 40 °C also yielded dinitro compounds (**9** and **10**) (Figure 1).

In ^{1}H nmr spectra the chemical shifts of the C15-H_2 protons were authoritative. The difference in the shifts of these protons was minimal in the case of the vincamine derivatives. On the other hand, this difference was considerable in the C-14 epimers (see: Experimental). The ^{13}C nmr chemical shifts are collected in Table I and in Fig. 1 for **11**. The interpretation of the data of non-substitued derivatives was published earlier [5]. The ^{1}H and ^{13}C signal assignments of compound **11** were supported by detailed nmr measurements. The two-dimensional carbon-proton correlation map of **11** (Fig. 2a) allowed the assignment of all CH units with the exception of the H-10/C(10) and H-12/C(12) pairs. Applying the semiselective INEPT (INAPT) [6] technique optimized for $J = 7$ Hz and $J = 3$ Hz C-H couplings, respectively, a correlation between the proton appearing at δ 8.45 and C(2) (134.8 ppm) was obtained. It follows that the signals at 8.45 and 8.73 correspond to H-12 and H-10, respectively. A series of INAPT measurements on H-15, H-12, H-10 and H-3 gave unambiguous assignments of signals C(14) and C(8), further of C(9), C(11) and C(13) (Fig. 2b).

* Compound **9** was prepared earlier — Zsadon, B.: personal communication.

Table I

^{13}C nmr spectra of compounds **3—10**
(Chemical shifts, δ, in ppm, relative to TMS)

Carbon	3[a]	4[a]	5[a]	6[b]	7[a]	8[a]	9[b]	10[b]
2	132.6	133.1[c]	136.4[c]	137.6[c]	132.2	132.6	134.9	136.9
3	59.1	58.9	59.5	59.0	59.1	58.8	58.9	58.8
5	50.4	50.4	51.2	50.7	50.8	51.0	49.7	50.0
6	16.4	16.2	19.7	19.2	16.7	16.6	18.7	18.5
7	107.0	107.4	105.6	104.4	106.1	106.6	105.9	106.3
8	133.6	134.6[c]	121.9	120.7	127.9	127.6	124.2	124.0
9	117.9	117.5	141.9	141.1	119.5	119.3	139.7	139.2
10	116.0	115.6	116.2	117.3	123.5	123.5	112.3	112.3
11	142.5	142.2	120.2	120.5	115.0	115.1	143.8	144.4
12	107.2	109.9	118.1	119.5	113.5	115.4	112.7	114.6
13	138.4	138.4	136.6[c]	138.3[c]	134.9	136.5	139.2	139.0
14	82.2	83.9	82.1	84.2	82.0	83.2	83.0	84.8
15	44.6	46.2	44.6	45.2	44.5	47.2	42.8	44.1
16	35.0	36.4	34.9	35.7	35.1	36.5	34.2	35.3
17	25.1	24.2	25.1	24.2	25.1	24.4	24.9	24.3
18	20.5	20.4	20.6	20.4	20.8	20.8	20.0	19.9
19	44.3	44.7	44.8	44.5	44.5	44.8	44.1	44.4
20	28.7	28.6	28.8	28.2	28.9	29.0	27.8	27.7
21	7.5	7.4	7.5	7.5	7.6	7.6	7.0	7.0
$COOCH_3$	54.5	53.4	54.5	53.1	54.5	53.6	53.4	53.0
$COOCH_3$	173.2	170.9	173.9	170.7	174.0	172.3	171.2	169.8

Solvents: a) $CDCl_3$; b) DMSO-d_6; c) tentative assignment

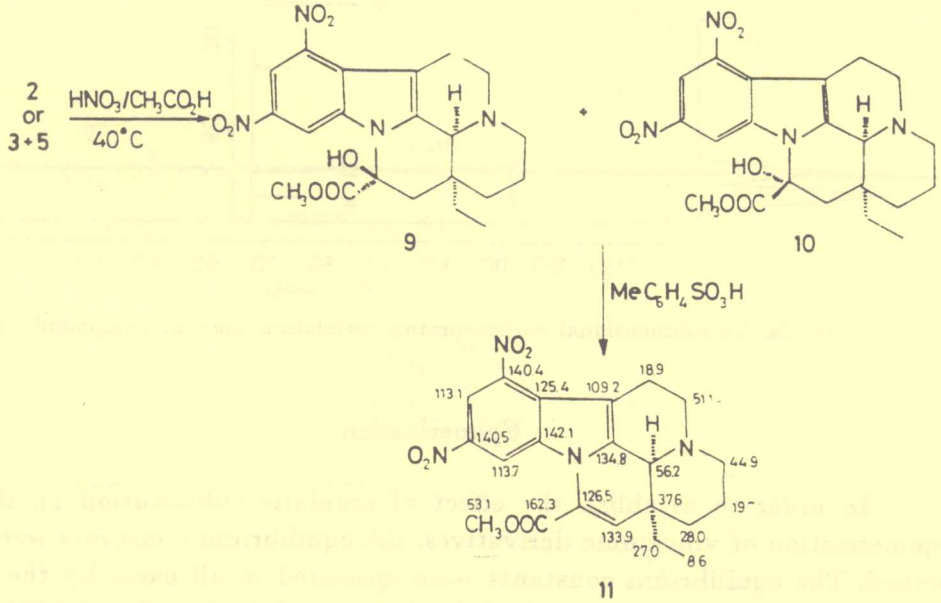


Fig. 1. Formation of dinitro derivatives. The ^{13}C chemical shifts of compounds *11* ($CDCL_3$, δ, in ppm, relative to TMS)

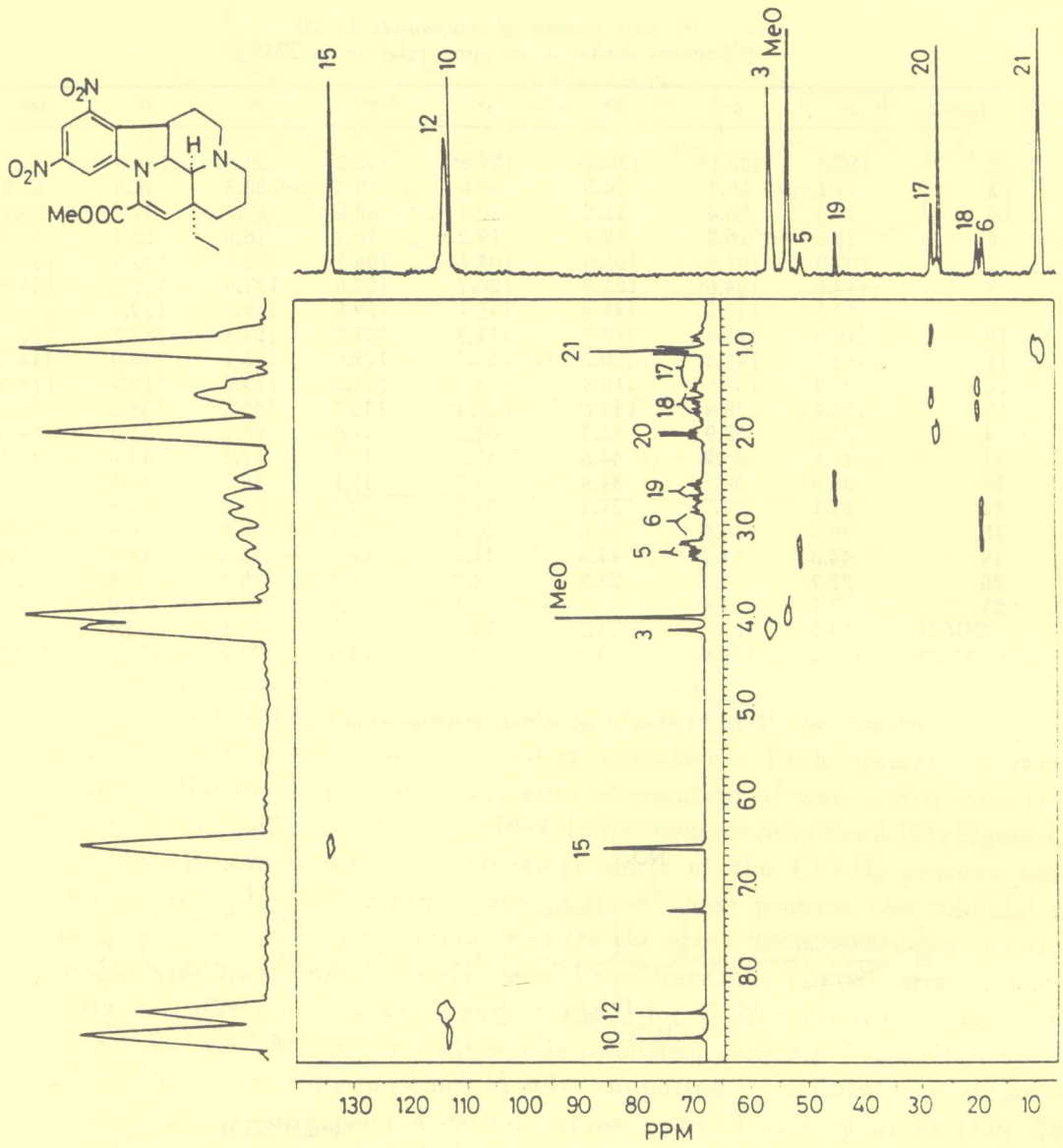


Fig. 2a. Two-dimensional carbon-proton correlation map of compound *11*

Epimerization

In order to establish the effect of aromatic substitution on the C-14 epimerization of vincamine derivatives, the equilibrium constants were determined. The equilibrium constants were measured in all cases by the quantitative uv-tlc densitometric method. In the cases of the **1** ⇄ **2** and **8** [7] ⇄ **7** [8 equilibria the reaction rates are low, thus these equilibrium constants were determined from the rate constants (see: Experimental). The compositions of

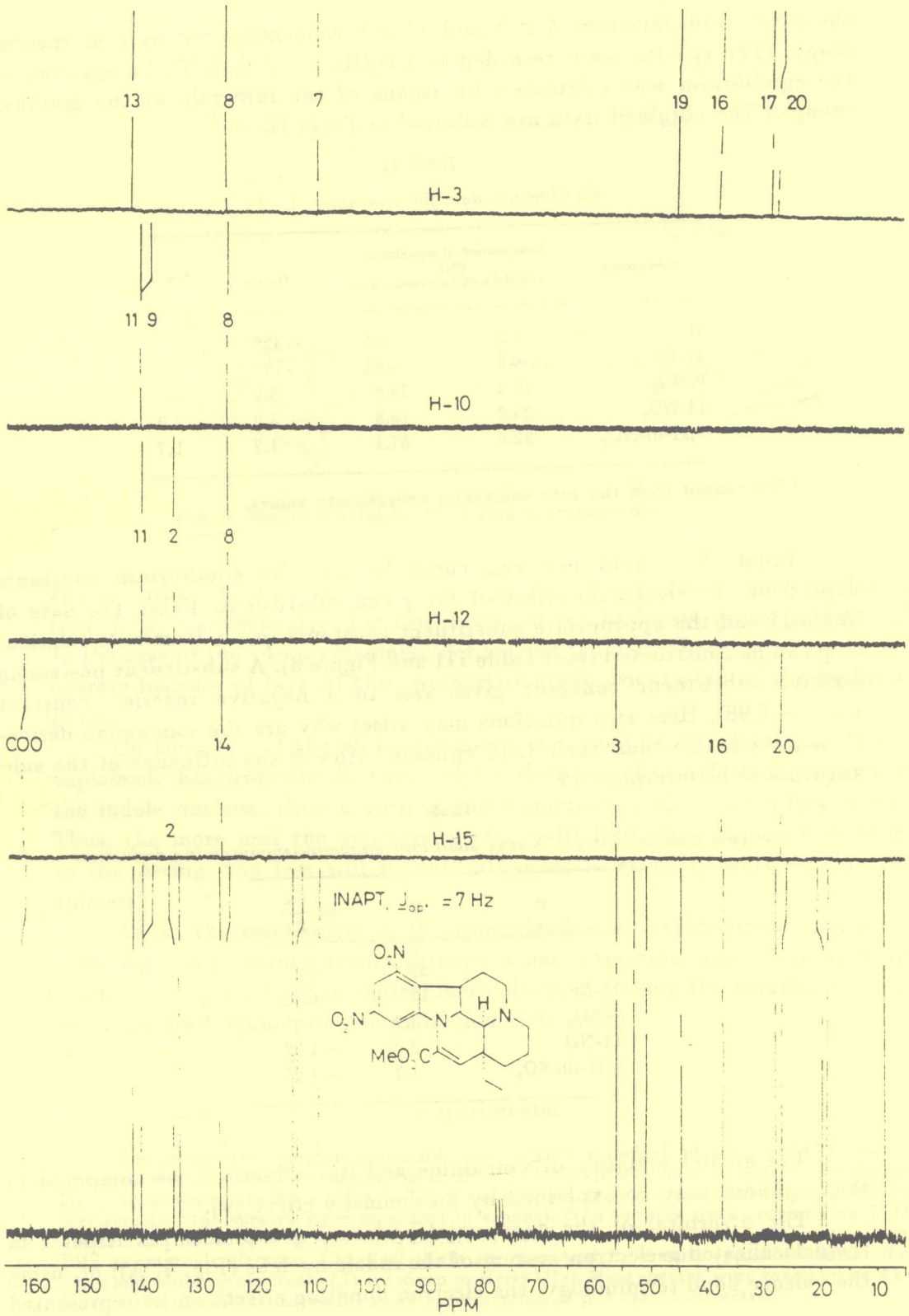


Fig. 2b. INAPT measurements for compounds *11*

the equilibrium mixtures **4** $\rightleftarrows$ **3** and **10** $\rightleftarrows$ **9** were measured by nmr spectroscopy. (The spectra were recorded in CD_3OD at 25 $\pm$ 1 °C. Composition of the equilibrium was calculated by means of the integrals of the methoxy groups.) The obtained data are collected in Table II.

Table II

Equilibrium data for compounds **1**—**10**

Substituent	Composition of equilibrium (%) 14-epivincamines	vincamines	K Uv-tlc	Nmr
H	~3	~97	~32[a]	
11-Br	~8	~92	~12[a]	
9-NO_2	20.4	79.6	3.9	
11-NO_2	25.2	74.8	3.0	3.0
9,11-di-NO_2	32.6	67.4	1.7	1.7

[a] Determined from the rate constants; approximate values.

From these data one can conclude that the equilibrium constants depend on the electronic effect of the given substituent. Using the data of Table II and the appropriate substituent constants (σ), a Hammett relationship can be constructed (see: Table III and Figure 3). A substituent possessing positive substituent constant gives rise to a negative reaction constant ($\varrho_e = -0.98$). Here two questions may arise: why are the vincamine derivatives more stable than their C-14 epimers? How is the influence of the substituents to be interpreted?

Table III

Hammett relationships for A-*ring substitued vincamine/epivincamine derivatives*

R	K	$\log \frac{K_R}{K_H}$
H	32	0
11-Br	12	−0.42
9-NO_2	3.9	−0.91
11-NO_2	3.0	−1.02
9,11-di-NO_2	1.7	−1.27

The greater stability of vincamine and its derivatives, as compared to their epimers, may be explained by an anomeric effect [9].

The σ^*-orbital of the *quasi-axial* hydroxyl group also participates in the delocalizated π-electron system of the indole nucleus (Fig. 4, A); or, using the valence bond terminology, the electron donating effect can be represented

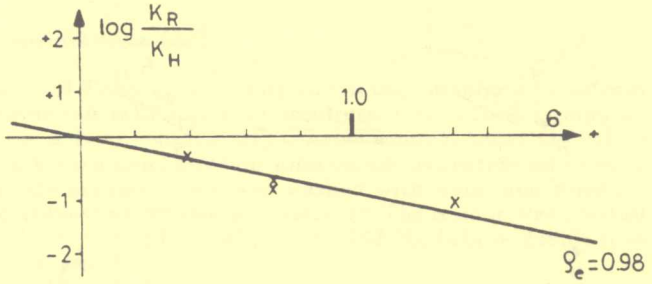


Fig. 3

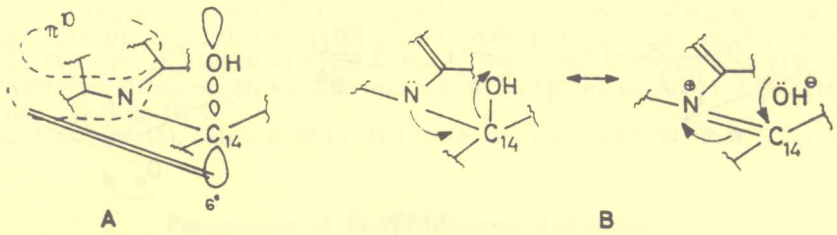


Fig. 4. Stability relation of vincamine/epivincamine derivatives

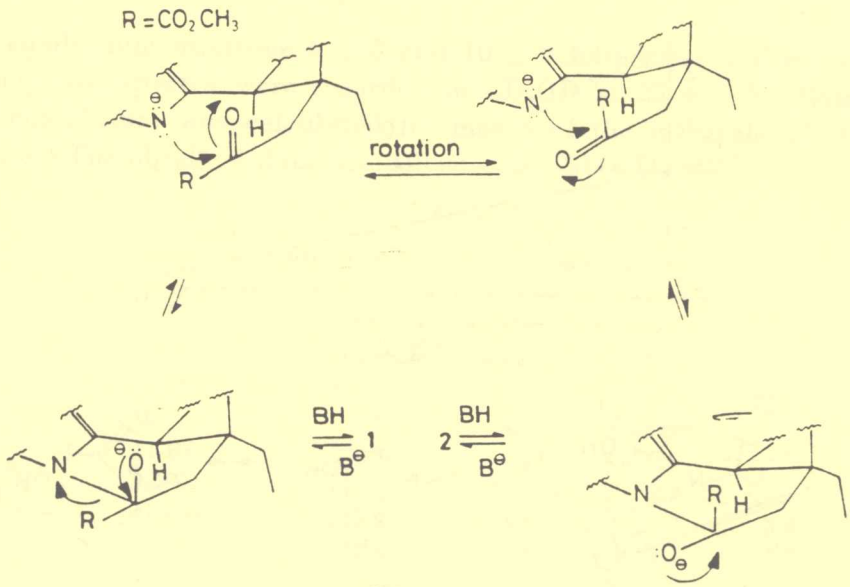
as a contribution to the double bond — no bond form of the resonance hybrid (Fig. 4, **B**). Consequently, the orientation of the hydroxyl group is essential. In the case of the 14-epivincamine derivatives the delocalization effect cannot operate because of lack of the appropriate steric orientation of the hydroxyl group.

On the basis of the above reasoning the substituent effects can also be explained. Electron-withdrawing effects decrease the π-electron density of the indole nucleus, thus hindering the formation of the "secondary bond". Thus, the more and the stronger electron-withdrawing groups are attached to the A-ring, the less will be the difference in stability between the two epimers.

As for the mechanism of the epimerization an explanation may be the following: ring-opening occurs through a base-catalyzed heterolytic cleavage of the N_1-C_{14} bond of the neutral molecule, thus making the rotation possible, providing both epimers on recyclization (Scheme 2).

Experimental

For preparative column chromatography Merck Kieselgel 60 was used. The optical rotations were measured in chloroform at 25 $\pm$ 2 °C. Ir spectra were recorded on a Specord IR 75 spectrometer in KBr pelletts. The uv absorption spectra were recorded on a UV-VIS spectrometer; the spectra were measured in ethanol. Nmr spectra were obtained on JEOL FX-100 and BRUKER AC-250 instruments in $CDCl_3$, CD_3OD and DMSO-d_6 solutions with TMS as internal reference. Chemical shifts are expressed in δ units (ppm, downfield from TMS) and coupling constants (J) are given in Hertz (Hz). Mass spectra were taken on an AEI-MS-902 (70 eV, direct insertion) mass spectrometer. M.p.'s are uncorrected.



Scheme 2

Preparation of the dinitro derivatives

(+)-9,11-Dinitrovincamine (9) and (—)-9,11-dinitro-14-epivincamine (10)

To a solution of a mixture of 9- and 11-nitrovincamine (3 and 5, in a ratio of about 1 : 1; 10 g; 25 mmol) in glacial acetic acid (100 mL), fuming nitric acid (40 mL; $d = 1.52$) dissolved in glacial acetic acid (40 mL) was added dropwise at 40 °C. The mixture was poured onto broken ice (800 g) and methylene chloride (200 mL) was added. The mixture was made alkaline (pH 8) by adding *conc.* aqueous ammonium hydroxide solution (270 mL). The organic layer was separated and the aqueous phase was extracted with methylene chloride (2 × 150 mL). The combined organic phase was washed with water (3 × 100 mL) and dried (Na_2SO_4). The filtrate was evaporated in vacuum and the residue (11 g) chromatographed on silica (500 g; eluent: 2000 mL of a mixture of ethyl acetate: cyclohexane 3/7). In this way two major fractions were separated. The component having the larger retention factor was compound **9** (5.3 g; 48%). M.p. 170—179 °C (from diisopropyl ether). $[\alpha]_D + 141.1°$ ($c = 0.2$).

Ir (KBr): 3450, 1740, 1530 cm^{-1}.

Uv (EtOH): 212, 314, 394 nm.

Ms (70 eV, 170 °C, *m/z* (%)): 444 (90, M^+), 443 (60), 426 (2), 398 (14), 385 (18), 384 (35), 383 (30), 374 (2), 367 (15), 357 (30), 342 (100, *M*-102), 327 (30), 314 (10).

^1H nmr ($CDCl_3$), δ: 1.05 (3H, t, $-CH_2CH_3$); 2.34 (1H, d, $J = 14.6$ Hz, 15-H); 2.50 (1H, d, $J = 14.6$ Hz, C15-H); 3.90 (1H, s, $-COOCH_3$); 4.10 (1H, s, C3-H); 8.78 (1H, d, C10-H); 8.55 (1H, d, C12-H); 1.3—3.4 (m, skeletal + $-CH_2CH_3$).

^{13}C nmr: see Table I.

$C_{21}H_{24}N_4O_7$ (444.43). Calcd. C 56.75; H 5.44; N 12.60. Found C 56.70; H 5.39; N 12.65%.

The component with the smaller retention factor was compound **10** (2.0 g; 18%). M.p. 141—144 °C (from acetone). $[\alpha]_D - 107.8°$ ($c = 0.2$).

Ir (KBr): 3450, 1750, 1510 cm^{-1}.

Uv (EtOH): 213, 313, 392 nm.

Ms (70 eV, 170 °C, *m/z* (%)): 445 (23), 444 (82, M^+), 443 (52), 429 (15), 427 (23), 426 (5), 415 (14), 401 (16), 398 (11), 397 (12), 385 (20), 384 (36), 383 (36), 367 (16), 357 (30), 342 (100, *m*-102), 327 (31), 325 (16).

^1H nmr ($CDCl_3$), δ: 1.05 (3H, t, $-CH_2CH_3$); 2.21 (1H, d, $J = 14.6$ Hz, C15-H); 2.99 (1H, d, $J = 14.6$ Hz, C15-H); 3.84 (1H, s, $-COOCH_3$); 4.10 (1H, s, C3-H); 8.79 (1H, d, C10-H); 8.69 (1H, d, C12-H); 1.3—3.4 (m, skeletal + $-CH_2CH_3$).

$C_{21}H_{24}N_4O_7$ (444.43). Calcd. C 56.75; H 5.44; N 12.60. Found C 56.81; H 5.39; N 12.54%.

(+)-9,11-Dinitroapovincamine (11)

A mixture of **9** and **10** (0.88 g; 2 mmol) and *p*-toluenesulfonic acid monohydrate (0.85 g;; 4.5 mmol) in benzene (40 mL) was refluxed for 8 h in a flask equipped with an automatic water separator (e.g. a Dean—Stark trap). After cooling, water (10 mL) was added, and the pH was adjusted to 8 with *conc.* aqueous ammonium hydroxide solution (1 mL). After extraction with benzene, the organic phase was washed with water and dried (Na_2SO_4). The filtrate was evaporated to dryness under reduced pressure. The residue was crystallized from methanol (10 mL) to afford **11** (0.52 g; 61%). M.p. 190—193 °C. $[\alpha]_D$ + 279.8° (c = 0.2).

Ir (KBr): 1700 cm^{-1}.

Uv (EtOH): 214. 317, 398 nm.

Ms (70 eV. 170 °C. *m/z* (%)): 426 (41, M^+), 409 (1.5), 397 (100, *M*-29), 381 (8), 380 (5), 367 (8), 363 (5), 356 (85, *M*-70), 352 (12), 340 (4), 338 (4), 326 (6), 311 (11), 305 (8), 264 (13).

^1H nmr ($CDCl_3$), δ: 1.06 (3H, t, $-CH_2CH_3$), 1.99 (2H, q, $-CH_2CH_3$). 2.55 (1H, td, H_{ax}-19), 2.71 (1H, dt, H_{eq}-19), 1.47 (1H, dm, H_{eq}-18), 1.76 (1H, qm, H_{ax}-18).0.92 (1H td, H_{ax}-19), 1.62 (1H, dt, H_{eq}-19), 6.61 (1H, s, H-15), 8.45 (1H, d, H-12), 8.73 (1H, d, H-10), 3.22 and 2.83 (1H, 1H, m. m, H_2-6), 3.22 and 3.35 (1H, 1H, m, m, H_2-5), 4.18 (1H, s, H-3).

^{13}C nmr: see Fig. 1.

$C_{21}H_{22}N_4O_6$ (426.42). Calcd. C 59.15; H 5.20; N 13.13. Found C 59.00; H 5.25; N 13.10%.

Preparation of 14-epivincamine derivatives

(+)-9-Nitro-14-epivincamine (6)

A solution containing 9-nitrovincamine (**5**) (1.1 g; 3 mmol) in a mixture of methanol (40 mL) and aqueous ammonium hydroxide (1 mL) was refluxed for 4 h. The solution was then concentrated under reduced pressure to 10 mL, and allowed to crystallize to recover some of the starting material (0.4 g). The mother liquor was evaporated to dryness and chromatographed on a column of silicagel (40 g; eluent: 300 mL of a mixture of chloroform : methanol 9/1). The collected eluates were evaporated in vacuum and the residue was crystallized from acetone (3 mL) to afford **6** (0.2 g; 18%). M.p. 112—115 °C. $[\alpha]_D$ + 50° (c = 0.2).

Ir (KBr): 3450. 1750, 1510 cm^{-1}.

Uv (EtOH): 213. 312, 388 nm.

^1H nmr ($CDCl_3$), δ: 0.90 (3H, t, $-CH_2CH_3$), 2.15 (1H, d, C15-H); 2.65 (1H. d, C15-H); 3.74 (1H, s, $-COOCH_3$); 3.97 (1H, s, C3-H); 7.90 (1H, dd, C10-H); 7.14 (1H, t, C11-H); 7.61 (1H, dd, C12-H); 1.2—3.4 (m, skeletal + $-CH_2CH_3$).

^{13}C nmr: see Table I.

Compounds **4** and **8** were prepared analogously to the above procedure.

(—)-11-Nitro-14-epivincamine (4)

Yield: 25%. M.p. 124—126 °C. $[\alpha]_D$ — 148.8° (c = 0.2).

Ir (KBr): 3450. 1750. 1510 cm^{-1}.

Uv (EtOH): 214. 310, 388 nm.

^1H nmr ($CDCl_3$). δ: 0.90 (3H, t. $-CH_2CH_3$); 2.09 (1H, d, J = 14 Hz. C15-H_{ax}); 2.46 (1H, d. C15-H_{eq}); 3.76 (1H, s, $-COOCH_3$); 7.35 (1H, d, J = 8.8 Hz, C9-H); 7.96 (1H. dd, J = 8.8 and 2 Hz, C10-H); 8.26 (1H, d, J = 2 Hz, C12-H).

^{13}C nmr: see Table I.

(+)-11-Bromo-14-epivincamine (8)

Yield: 3%. M.p. 143—146 °C. *Lit.* [7] m.p. 136 °C (decomp). $[\alpha]_D$ + 31.9° (c = 0.2).

Ir (KBr): 3450, 1755, 1510 cm^{-1}.

Uv (EtOH): 253. 284 nm.

^1H nmr ($CDCl_3$). δ: 1.88 (3H, t, $-CH_2CH_3$); 3.75 (3H, s, $-COOCH_3$); 3.75 (1H, s, C3-H. overlap); 2.00 (1H. d, J = 14.6 Hz, C15-H); 2.60 (1H, d, C15-H); 7.10—7.60 (3H, m. Ar*H*); 1.1—3.3 (12H, m. skeletal + $-CH_2CH_3$).

^{13}C nmr, see: Table I.

Determination of the equilibrium and rate constants

The equilibrium and rate constants were determined by means of a High-Spead Chromato Scanner (Shimadzu CS-920) using Merck TLC (Art. 5553) plates. The tlc spots were taken at 20 mm distances. The scan parameters were: $X = 12$ mm; $Y = 15$ mm; linearizer = 1. The measuring wave-lengths were 388 nm for **3** and **4**, 390 nm for **5** and **6**, 282 nm for **7** and **8**, 392 nm for **9** and **10**, and 279 nm for **1** and **2**.

Concentrations were determined from the peak area data using external standards (pure epimers **1**—**10**, respectively, spotted just after dissolving).

For the determination of the equilibrium and rate constants methanolic solutions ($5 \cdot 10^{-3}$ mol/L) were used at 25 ± 1 °C. Of these solutions 2 μL was applied onto the tlc plates.

The concentrations were measured at different times, until no change was observed. The composition of the equilibrium state was established from the last measurement.

For **1** $\rightleftharpoons$ **2** and **7** $\rightleftharpoons$ **8** the composition of the equilibrium state was established from the equilibrium constant that was determined from the rate constants. The rate constants were calculated by means of a simple first-order equation: $\ln (a_0 - x) - \ln a_0 = -kt$. Thus the rate constants are [1/h]: $k_{1\to 2} = 3.06 \cdot 10^{-3}$, $k_{2\to 1} = 9.58 \cdot 10^{-5}$, $k_{8\to 7} = 1.41 \cdot 10^{-3}$, $k_{7\to 8} = 1.11 \cdot 10^{-4}$.

*

The authors are grateful to Dr. J. Tamás and Dr. M. Mák for the mass spectrometic measurement, to Dr. A. Nemes (Richter Gedeon Ltd.) for compound **1**, and to Mrs. K. Welker for technical assistance.

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NITRO APOVINCAMINIC ACID DERIVATIVES: PREPARATION AND BIOLOGICAL EFFECTS

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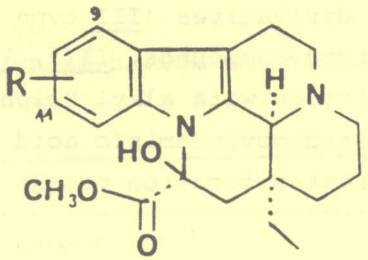
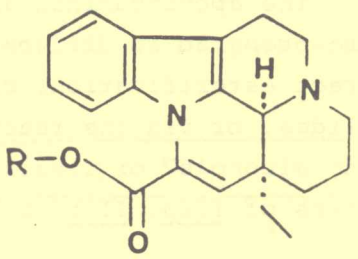
PREPARATION

As reported in the literature (ref.1) nitration of vincamine (Ia) results in a mixture of isomeric nitrovincamines Ib and Ic. While 11-nitrovincamine (Ic) can be separated by crystallization, the 9-nitro-isomer (Ib) is isolated from the mother liquor by column chromatography.

We wish to report our recent findings on the investigation of nitration of vincamine (Ia) as well as of the apovincaminic acid derivatives, IIa, IIb.





Ia R=H (vincamine)
Ib R=9-NO_2
Ic R=11-NO_2

IIa R=H (apovincaminic acid)
IIb R=ethyl (vinpocetin*)

* Manufactured by Gedeon Richter Ltd., Hungary

The ratio of the isomeric 9/11-nitro compounds was determined in the crude product. As shown (see Table 1), the ratio of isomers depended on the substrate. In case of vincamine (Ia) the formation of 9-nitro-isomer (Ib) was found to be poor, while nitrating apovincaminic acid derivatives, IIa and IIb, the 9-nitro compounds (IIIa and IIIc respectively) were obtained in higher proportion.

These results indicate some steric hidrance of the nitration at position 11 in case of IIa and IIb.

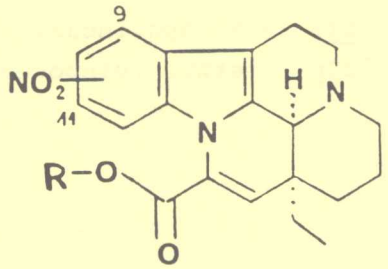
TABLE 1

The ratio of the isomeric 9/11 nitro compounds in the crude product prepared in acetic acid with nitric acid at 16°.

Substrate	9-isomer (in %)	11-isomer
Vincamine (Ia)	28	72
Ethyl apovincaminate (IIb)	47	53
Apovincaminic acid (IIa)	46	54

The isomeric nitroapovincaminic acids were preferably separeted by crystallization of the corresponding nitrate salts (ref.2).

The apovincaminic acid ester derivatives (III type compounds) were prepared in different ways; from compounds, IIIa, IIIb by direct esterification, or by alkylation with alkyl sulphate or halides, or via the reaction of nitroapovincaminic acid halides with alcohols, or finally by transesterification of the methyl-esters of IIIa, IIIb ref. 3).



IIIa	9-NO_2	R=H
IIIb	11-NO_2	R=H
IIIc	9-NO_2	R-ethyl
IIId	11-NO_2	R=ethyl
IIIe	9-NO_2	R=n-propyl
IIIf	9-NO_2	R=n-octyl
IIIg	9-NO_2	R=2-acetoxy-ethyl

BIOLOGICAL EFFECTS

The III type derivatives have shown valuable therapeutic properties, namely vasodilatory spasmolytic and antihypoxic effects.

The vasodilatory effect was studied in anaesthesized dogs. Electromagnetic flow meters were used for measuring the blood flow in the femoral and internal carotid artery. Data are shown in Table 2.

TABLE 2
Circulatory effects (change in %) at intravenous doses of 1 mg/kg body weight.

Compound	Carotid artery flow	Femoral flow
IIb	+30	+15
IIIc	+95	0
IIId	+10	0
IIIf	0	0

The spasmolytic activity of the compounds was determined on isolated guinea pig ileum. The results are summarized in Table 3.

TABLE 3
Inhibition of barium chloride induced contraction of guinea pig ileum

Compound	relative activity	ED_{50} µg/ml
papaverine	1.0	5.4
IIb	2.7	2.0
IIIc	5.4	1.0
IIIg	13.5	0.4
IIIe	27.0	0.2

The antihypoxic activity was measured on conscious mice under normobaric hypoxia. The compounds were intraperitoneally administered in a dose of 50 µg/kg (see Table 4).

TABLE 4

The antihypoxic effect on conscious mice under normobaric hypoxia

Compound	Time of survival min.	Increase of survival in %
control	6.0 ± 1.0	-
Ia	6.1 ± 1.3	2
IIIc	13.4 ± 2.4	123
IIIg	10.1 ± 3.5	68
IIId	11.0 ± 3.4	83

CONCLUSION

On the basis of the above investigations it can be stated that the biological activity of vincamine derivatives is preferably influenced by substitution with a nitro group at ring "A". The 9-nitro-derivative proved to be more active than the 11-nitroisomer. The cerebral vasodilating effects decreased when long chain alkyl esters were introduced. The IIIe propyl ester has the highest antispasmolytic activity.

ACKNOWLEDGEMENT

We wish to thank our pharmacologist-coworkers, Drs. L. Szporny, E. Kárpáti, É. Pálosi, Zs. Szombathelyi and M. Riesz for their work and results.

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Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

THE STRUCTURE INVESTIGATION OF A NEW PRODUCT FORMED IN THE COURSE OF NITRATION OF APOVINCAMINIC ACID ETHYL ESTER BY NMR METHODS*

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(Received 26 September 1988)

ABSTRACT

A new 2,7-dihydro-indole derivative formed during the nitration of apovincaminic acid ethyl ester (Cavinton®), has been studied by ^{1}H and ^{13}C NMR spectroscopy. Homo- and heteronuclear NOE (nuclear Overhauser effect) difference measurements, together with homo- and hetero-shift correlation experiments allowed the complete assignment of the NMR spectra, and the elucidation of the constitution and stereochemistry of the molecule.

INTRODUCTION

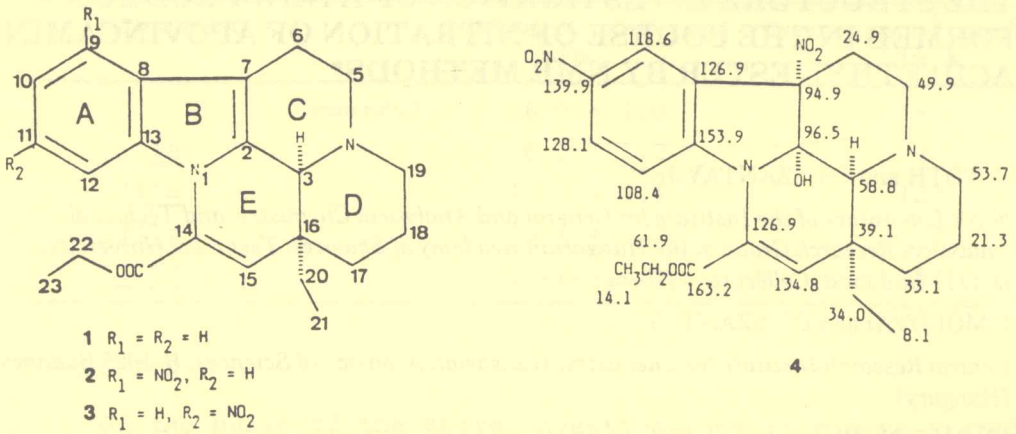
Alkaloids with the eburnane skeleton have remarkable biological activity [1]. This has drawn attention not only to the syntheses of these natural products, but also to the preparation of differently modified synthetic derivatives. The corresponding structure investigations thus gained special importance in the goal of understanding structure/activity relationships. Apovincaminic acid ethyl ester (**1**) is on the market under trade names Cavinton® or Calan®, and is used because of its specific cerebral vasodilator activity. Whilst preparing

*Syntheses of Vinka Alkaloids and Related Compounds, Part 40. For Part 39 see: I. Moldvai, G. Tóth, Cs. Szántay Jr., H. Kühne, A. Vedres and Cs. Szántay, J. Chem. Res., (S) (1988) 314, M (1988) 2423.

**On leave from the Chemical Works of Richter Gedeon Ltd.

0022-2860/89/$03.50

potentially bioactive derivatives, (**1**) was treated with a mixture of HNO_3 and CH_3COOH at -5 °C. After work-up 9-nitro- (**2**) [2], and 11-nitro- (**3**) [2] derivatives were isolated in the ratio of 1:1 (Scheme 1).



Scheme 1. Structure of compounds **1**–**4**. For compound (**4**), the ^{13}C chemical shifts measured at 100 MHz ($CDCl_3$, $\delta_{TMS} = 0.0$ ppm) are also depicted.

When the nitration was performed at ambient temperature, in addition to (**2**) and (**3**) a dinitro-derivative (**4**) was isolated in 10% yield. The structure elucidation of (**4**), especially because of the stereochemical problems introduced by the two additional asymmetric centres, required thorough NMR investigations using, for example, hetero- and homo-correlated two-dimensional spectra together with hetero- and homo-nuclear NOE difference measurements.

RESULTS AND DISCUSSION

Some preliminary information about the structure of compound (**4**) was obtained from the mass and IR spectra. The mass spectrum revealed that in addition to the NO_2 substitution of ring *A*, addition of the elements of the $HONO_2$ unit also took place. The strong signal in the IR spectrum at 3490 cm^{-1} clearly indicated the presence of an OH group. Additional information about the constitution of the molecule was gained from the ^{13}C and ^1H NMR spectra. (^{13}C chemical shifts are indicated in Scheme 1, ^1H chemical shifts and coupling constants are collected in Table 1.) A comparison of the ^{13}C NMR spectrum of (**4**) with that of apovincaminic acid ethyl ester [3] reveals that the δ 130.8 ppm (C2) and δ108.4 ppm (C7) signals characteristic for the indole chromophore in the latter are shifted to δ 96.5 and 94.9 ppm in compound (**4**). This indicates that the HO–NO_2 addition took place on the C2–C7 double bond. The coupling pattern of the aromatic signals in the ^1H NMR spectrum (see Table 1) clearly indicates that ring *A* was substituted either on C10 or C11. Additionally, careful consideration (see below) of the number of signals,

TABLE 1

^{1}H chemical shifts (ppm) and coupling constants (Hz) for compound (4) (400 MHz, $CDCl_3$, $\delta_{TMS} = 0.0$ ppm)

Proton	δ	^3J	Value (Hz)	^2J	Value (Hz)	^4J	Value (Hz)
H3	3.02	$5_a,6_a$	11.4	5,5	11.2	9,11	2.2
H_e5	~2.50	$5_a,6_a$	7.2	6,6	14.0	3,15[b]	1.0
H_a5	2.41	$5_e,6_a$	8.8	17,17	13.5		
H_e6	2.55	$5_e,6_e$	1.0	18,18	14.5		
H_a6	2.88	$17_a,18_a$	13.5	19,19	11.5		
H9	7.90	$17_a,18_e$	3.0	20,20	13.8		
H11	8.12	$17_e,18_a$	[a]	22,22	14.4		
H12	6.36	$17_e,18_e$	[a]				
H15	6.33	$18_a,19_a$	11.5				
H_e17	1.72	$18_a,19_e$	[a]				
H_a17	1.41	$18_e,19_a$	2.5				
H_e18	1.36	$18_e,19_e$	[a]				
H_a18	1.09	11,12	9.0				
H_e19	~2.50	20,21	7.5				
H_a19	1.91	22,23	7.2				
H_e20	1.65						
H_a20	1.90						
H_a21	0.91						
H_e22	4.30						
H_a22	4.35						
H_a23	1.33						

[a]These coupling constants cannot be accurately measured either because they are unresolved, or disguised by overlappings. [b]This coupling correlation was identified from a decoupling experiment.

their multiplicities and characteristic chemical shifts in the ^{1}H and ^{13}C spectra led to the structure as shown in Scheme 1. However, determination of the exact positions of the OH and NO_2 groups still remained undefined at this stage, and required definite signal assignments. Two-dimensional (2D) H–H and C–H shift correlated spectra were therefore recorded, together with homo- and hetero-nuclear NOE measurements.

ASSIGNMENTS AND CONSTITUTION

In the aliphatic region of the 400 MHz ^{1}H NMR spectrum the H3, $H_2$22, $H_3$23, $H_2$20 and $H_3$21 signals could be readily assigned on the basis of their characteristic chemical shifts, multiplicities and H–H correlations revealed by the 2D COSY-45 [4] spectrum. Among the $H_{a,e}6$, $H_{a,e}5$ and $H_{a,e}19$ protons (resonating in the relatively low-field part of the aliphatic region (δ 1.8–3.0 ppm), the well separated H_e6 signal can be easily identified by exploiting the

fact that in the 2D C–H COSY spectrum [5], the C19 and C5 carbons adjacent to N4 are significantly low field of C6. Identification of the closely spaced H_e6, $H_{a,e}5$ and H_e19 signals (δ 2.35–2.58 ppm) was carried out through simple decoupling measurements (using H_a6 as a starting point), and 1D NOE difference experiments (Table 2) (see for example, the large NOE enhancement on H_e6 upon irradiating H_a6). Assignment of H_a19, $H_{a,e}18$ and $H_{a,e}17$ was then straightforward by considering their multiplicities and tracing their coupling network in the 2D spectra (see also the geminal H–H correlations in the C–H correlated contour plot). It is interesting to note the anisochronous character of the $H_{x,y}22$ protons ($\Delta\delta \sim 0.05$ ppm); this is surprising considering their long distance from the nearest asymmetric centre.

By exploiting the above ^1H assignments, the C–H correlation map allowed the direct identification of all carbons attached to protons. In order to prove the C2 position of the OH group, it was particularly important to assign unambiguously the closely spaced C2 (δ 96.5 ppm) and C7 (δ 94.9 ppm) signals. This was achieved by a 1D heteronuclear NOE difference measurement, which implements the fact that low power irradiation of suitable narrow ^1H peaks results in NOE enhancement in the neighbouring quaternary carbons, positioned two bonds from the irradiated proton [6]. Upon irradiating H3, the enhancement of the C2 signal (Fig. 1) allowed the definite assignment of the latter. The assignment of C2 and C7 was also corroborated by the measurement of a COLOC [7] spectrum (optimized for 6 Hz long-range C–H couplings), revealing the H_e5–C7 and H_e6–C2 *trans* ^3J(C,H) correlations. After an excess of a 1:1 mixture of H_2O/D_2O was added [8] to the solution of **4**, the C2 signal doubled ($\Delta\delta \sim 0.1$ ppm) due to the deuterium isotope shifts while other signals remained unaffected, thus proving the C2 position of the OH group.

TABLE 2

Results of proton-proton one-dimensional NOE difference experiments on compound (**4**)

Irradiated proton	Observed NOE (%)
H3	H_a19 (2%), H_x20 (4%), H_y21 (5%), H_a17 ($\sim$2%)[b]
H_a6	H_e6 (13%)
H_a19	H3 (2%), H_e19 (12%), H_a17 (3.5%)
(H_y20)[a]	(H_x20 (9%), H15 (2.5%), H_y21 (5%))
H_x20	H_y20 (10%), H3 (4%), H_y21 (3.5%)
H_a17[c]	H_y21 (m), H_x20 (m), H_e17 (s), H_a19 (m), H3 (m)

[a]Irradiation of H_y20 is the accidental result of its very close proximity to the target signal (H_a19). [b]Precise measurement of this enhancement was not possible due to the close proximity with the distorted H_y23 signal in the difference spectrum. [c]This measurement was carried out at 500 MHz to achieve better selectivity; still, due to the strong overlappings, the resulting enhancements cannot be accurately measured, therefore they are denoted as medium (m, ~4–9%) or strong (s, >9%).

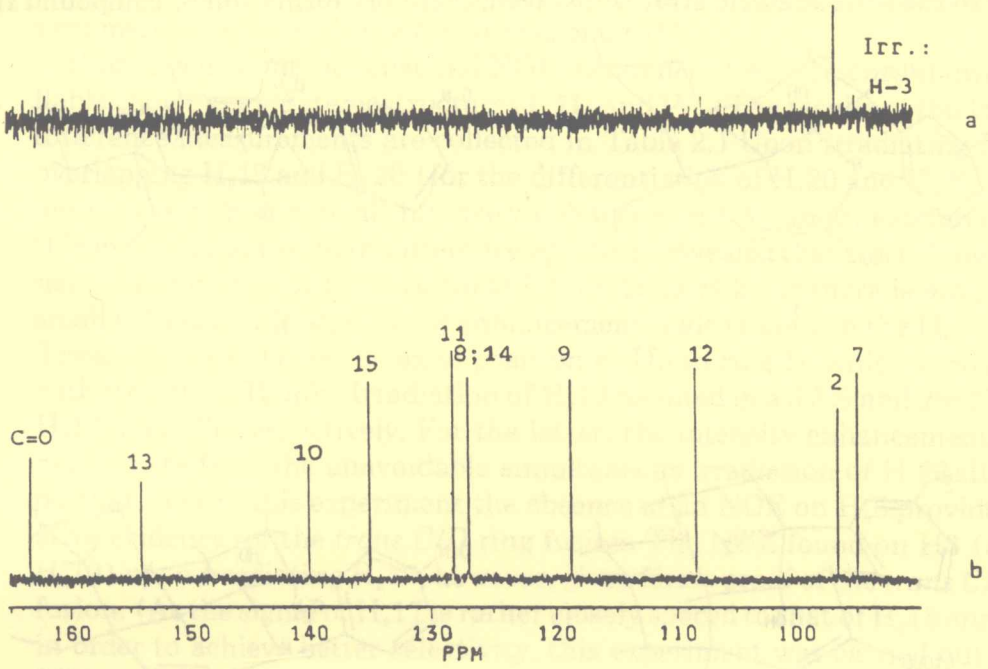


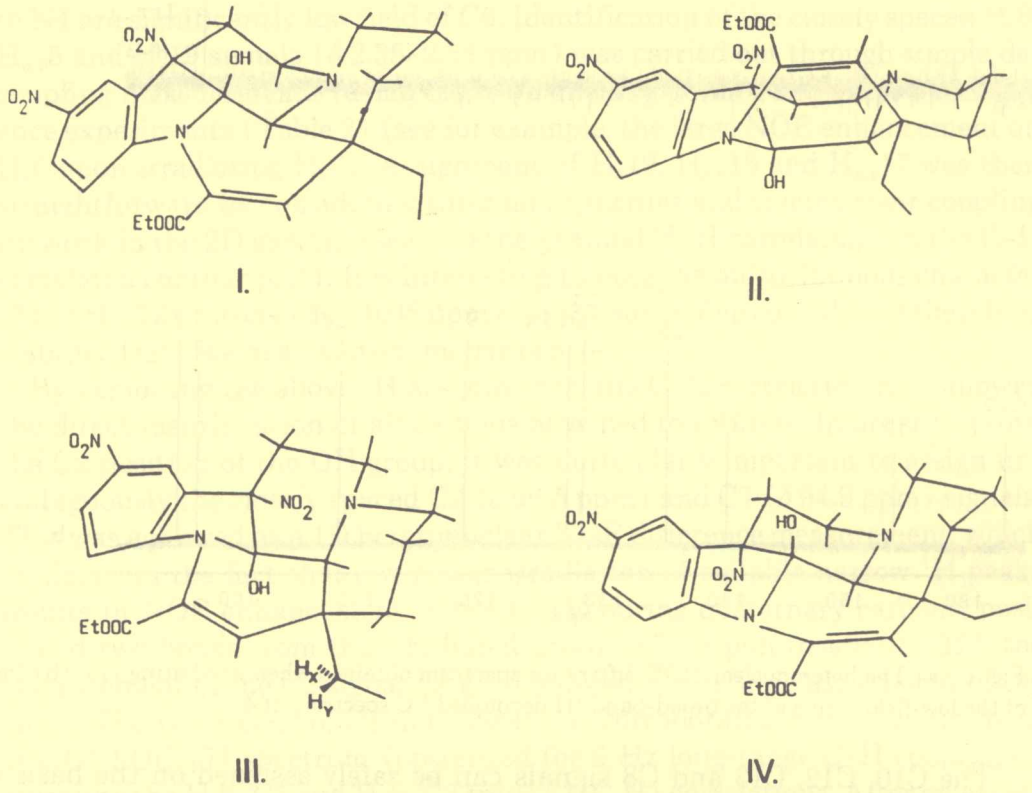
Fig. 1. (a) The heteronuclear NOE difference spectrum obtained when irradiating H3. (b) Part of the low-field region of the broad-band ^{1}H decoupled ^{13}C spectrum of **4**.

The C10, C12, C13 and C8 signals can be safely assigned on the basis of comparisons with suitable model compounds containing the 2,3-dihydro-indole moiety [9] and by considering the aromatic ^{13}C shift increments of the NO_2 group [10], irrespective of whether the latter is in position 10 or 11. The fact that in the ^{1}H coupled ^{13}C spectrum the C12 signal shows no $^{3}J(C,H)$ "*meta*-coupling" clearly indicates the C10 position of the aromatic NO_2 group. Using the C12–H12 correlation as a starting point, the assignments of the aromatic ^{1}H and ^{13}C carbon signals are obvious. The fact that H12 has no *meta* H–H coupling partner again points to the C10 position of the NO_2 group. The assignments of the C8, C10 and C13 quaternary carbon signals are also supported by the COLOC spectrum, revealing the C8–H12, C10–H12 and C13–H11 correlations.

STEREOCHEMISTRY

Assuming that the relative configurations of C3 and C16 were not affected during the reaction, due to the introduction of two additional asymmetric centres (C2 and C7), four possible diastereoisomers must be taken into consideration (Scheme 2). From model studies, each diastereoisomer can be readily associated with either a predominant *cis* or *trans* character of the *C/D* ring fusion, as shown in Scheme 2. Structure **II** seems to be rather unfavourable

due to the serious steric strains involved; therefore formation of compound **II**



Scheme 2. Stereo structures of diastereoisomers I–IV. Unlabelled bonds denote H.

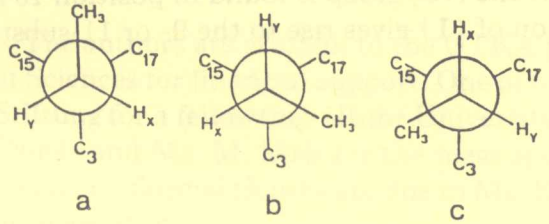
can be regarded as very unlikely. In structures **I** and **IV** the H_a19 and H_a17 protons are both involved in strong steric repulsions with the OH group; thus compound **III** seems to be the thermodynamically most stable diastereoisomer.

During the investigation of the stereostructure of compound (**4**), information was collected which independently pointed to the presence of isomer **III**. The relatively small absolute value of $^2J(H_a5, H_e5)$ (11.2 Hz) indicates the presence of the antiperiplanar effect of the nitrogen lone pair [11], which points to a *trans C/D* ring fusion, and therefore to structure **III** (assuming that structure **II** can be ignored). It is well known that the *cis/trans* character of the quinolizidine skeleton is sensitively reflected by the ^1H chemical shift of the bridgehead proton [12]. By assuming that the shift increments of the OH and NO_2 groups have only small effects on δ(H3) [13], its δ value of 3.02 ppm is more likely to be in accord with a *trans C/D* ring fusion, which again corresponds with structure **III**. (In **II**, H3 would be expected to resonate at much lower field, mainly because of the strong van der Waals interaction with the OH group.) Structure ***III*** is further confirmed by the presence of the ^4J(H3, H15) ~ 1 Hz coupling (this is clearly resolved on the H15 signal at 400 MHz),

which can be attributed to the presence of the "W" pathway between these protons, characteristic only for stereoisomer **III**.

Homonuclear one-dimensional NOE difference measurements allowed a reliable choice among stereostructures **I, III** and **IV**. (The results of the 1D NOE difference measurements are collected in Table 2.) Upon irradiating H3, the overlapping H_a19 and H_y20 (for the differentiation of H_x20 and H_y20, see below) signals show a small intensity enhancement. A careful examination of this multiplet in the NOE difference spectrum revealed that the enhanced signal is mainly that of H_a19 (a contribution from H_y20, if there is any, is very small). A small, but significant enhancement is also found on the H_a17 signal. These results indicate the axial position of H3 in ring *D*, which corresponds with structure **III** only. Irradiation of H_a19 resulted in a 3.5% and 2% NOE on H_a17, and H3, respectively. For the latter, the intensity enhancement might partly arise from the unavoidable simultaneous irradiation of H_y20. It is important, that in this experiment the absence of an NOE on H_a6 provides negative evidence for the *trans C/D* ring fusion. The NOE found on H3 (and on H_a19) upon irradiating H_a17, however, gives direct proof of the *trans C/D* ring fusion. (As the signal of H_a17 is rather closely spaced to that of H_e18 and H_323, in order to achieve better selectivity, this experiment was carried out at 500 MHz.) Neither the irradiation of H_x20 nor that of H_y20 resulted in NOE on H_a18, which again gives negative evidence for the presence of compound **III**, when considering that it is only this structure which possesses an equatorial C20–H_2 methylene group.

Although the H_220 methylene protons are diastereotopic, their rather large chemical shift difference ($\Delta\delta = 0.25$ ppm) indicates that the populations of the possible conformations around the C16–C20 bond (Scheme 3) are very differ-



Scheme 3. Possible staggered conformations around the C16-C20 bond.

ent. The NOE data revealed that conformations **a** and **b** participate in the conformational equilibrium with a comparable ratio. The contribution of conformer **c** is very unfavoured due to the steric repulsion between H_321 and the OH group. The presence of conformer **b** is indicated by the NOE between H3 and H_321, and by the enhancement found on H15 upon saturating H_y20. The contribution of conformer **a** is proven by the NOE found between H_a17 and H_x20, and between H3 and H_x20. The H_x20 and H_y20 signals can be assigned unambiguously according to these results.

The presence of most of the NOEs in the 1D difference spectra discussed above has also been confirmed by recording a NOESY spectrum [14] at 400 MHz.

^{13}C NMR data also support structure **III**: it is known that in compounds containing the eburnane skeleton, the *cis-trans* isomerism of the *C/D* ring fusion is sensitively monitored by the ~10 ppm difference in δ(C19) in the two isomers. (In apovincaminic acid ethyl ester, for example, δ(C19) = 44.7 ppm [3], while in 3-*epi*-apovincaminic acid ethyl ester δ is 55.2 ppm [15] ($CDCl_3$).) Assuming that the constitutional differences in (**4**) with respect to apovincaminic acid ethyl ester will only affect δ(C19) very slightly, its value of 53.7 ppm reflects the *trans* character of the *C/D* ring fusion. It is characteristic that the C20 signal (δ = 34.0 ppm) shows more than 10 ppm downfield shift relative to its value in 3-*epi*-apovincaminic acid ethyl ester (δ = 21.6 ppm) [15]. This can be well explained by the fact that in the latter compound C20 experiences two additional *γ-gauche* interactions (with N1 and C18) relative to (**4**).

After these investigations had been completed, a single crystal X-ray measurement was also performed [16]; the result was in perfect agreement with the configuration and stereochemistry suggested on the basis of the NMR analysis.

The elucidation of the structure of compound (**4**) allowed a better insight into the mechanism of the reaction leading to this product. Although the addition of the elements of $HONO_2$ to the indole double bond in the case of very simple derivatives is already known [17], to the best of our knowledge the stereochemistry of the compounds obtained was not investigated. In our case the fact of the *cis*-addition can be rationalized by steric approach control. The addition of $HONO_2$ is followed by nitration and not vice versa. This assumption is substantiated by the fact that the NO_2 group is found in position 10 in compound (**4**), while direct nitration of (**1**) gives rise to the 9- or 11-substituted products (**2**) or (**3**).

EXPERIMENTAL

Spectroscopy

All the NMR spectra were recorded in the PTF mode, with internal deuterium lock at ambient temperature (298 K), in $CDCl_3$ using TMS as internal standard. The ^1H and ^{13}C NMR measurements were performed at 400 and 100 MHz, respectively, on a Bruker AM-400 spectrometer. One homonuclear NOE difference measurement was carried out at 500 MHz, on a Bruker AM-500 instrument. The ^1H chemical shifts and coupling constants were calculated as first-order spectra at 400 MHz. NOE difference and two-dimensional experiments were recorded by using the Bruker software package. Delay times of 3 s

and 25 s were used for homonuclear and heteronuclear NOE measurements, respectively. The mass spectrum was recorded on an AEI-MS-902 spectrometer. The IR spectrum was measured on an NIC 7199 instrument.

Syntheses

(−)2.7-Dihydro-7α, 10-dinitro-2α-hydroxy-eburnamenine(3α,16α)-14-carboxylic acid ethyl ester (**4**) was synthesized as follows. To a solution containing 12 g (34.3 mmol) of (+)-apovincaminic acid ethyl ester in glacial acetic acid (120 ml), 12 ml of fuming nitric acid ($d=1.52$) dissolved in 48 ml of glacial acetic acid was added dropwise at room temperature, and the mixture was stirred for 0.5 h. The reaction mixture was poured into 400 g of broken ice, and chloroform (200 ml) was added. The mixture was alkalized to pH 8 by adding concentrated aqueous ammonium hydroxide solution. The organic layer was separated, the aqueous phase was extracted with chloroform (4×25 ml), and the combined organic phase was washed with water (5×20 ml) and dried (Na_2SO_4). The filtrate was evaporated in vacuo and the residue (12.5 g) was chromatographed on silica (Kieselgel 60 (Merck), 700 g; eluent, 500 ml ethyl acetate, 500 ml of a 9/1 mixture of ethyl acetate/cyclohexane, 3000 ml of a 8/2 mixture of ethyl acetate/cyclohexane; pressure 3 bar). The collected eluates were evaporated in vacuo and the residue (1.9 g, 12%) was crystallized from isopropanol to afford (**4**) (1.6 g, 10%). IR (KBr), 3490 cm^{-1}; (νOH), 2820, 2765 cm^{-1} (Bohlmann bands). MS: *m/z* 459 (27, M+H), 457 (6.3 M−H), 443 (2.4), 441 (2.2), 428 (1.9), 412 (100, M−46), 396 (39), 394 (22), 383 (9.8), 382 (16), 366 (16).

ACKNOWLEDGEMENTS

The authors are grateful to the OTKA program of the Hungarian Academy of Sciences for financial support. One of us (G. T.) thanks the A. v. Humboldt Stiftung for a fellowship (Ruhr University, Bochum). We wish to thank Dr. J. Tamás and Ms. M. Mák for the mass spectrum, and Dr. S. Holly for the IR spectrum. Special thanks are due to Ms. K. Welker and Ms. E. Szabó for technical assistance.

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VINCA-ALKALOIDOK ÉS SZÁRMAZÉKAIK REAKCIÓI JÓDDAL

Synthesis of Vinca Alkaloids and Related Compounds. Part 39.[1] Formation of Phenazine Derivatives from Vinca Alkaloids

J. Chem. Research (S), 1988, 314–315
J. Chem. Research (M), 1988, 2423–2441

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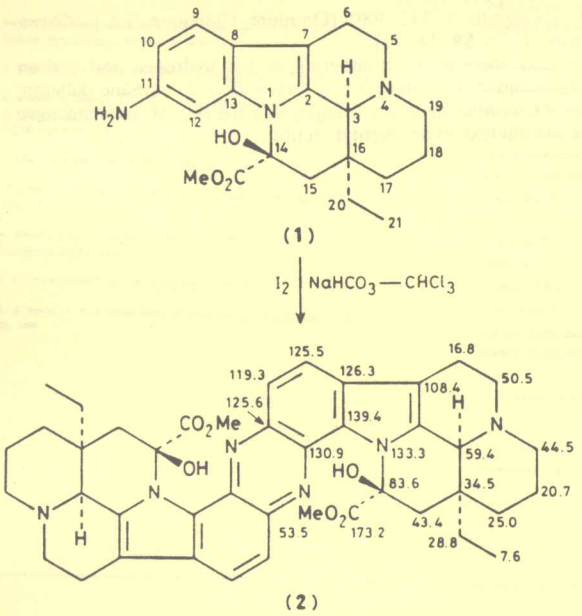
A unique formation of phenazine derivatives of some indole alkaloids has been discovered. Structural elucidation of the new compounds by n.m.r. spectroscopy is discussed.

In the course of our studies aimed at finding structure–bioactivity relationships in the Vinca alkaloids field, the iodination of (+)-11-aminovincamine (**1**)[2] was performed. When (**1**) was treated with iodine in a mixture of chloroform and saturated aqueous $NaHCO_3$ at room temperature for 2 h, instead of the expected iodo derivative, a red crystalline substance (**2**) (30% yield) was obtained (Scheme 1). To the best of our knowledge no such direct formation of phenazines through iodination of aromatic amines has yet been reported in the literature.[3] One possible reaction mechanism involves a step in which the iodo compound (**3**) is formed which subsequently affords, by elimination of hydrogen iodide, the dihydrophenazine derivative (**4**). Finally, the latter compound is then aromatized by iodine to the end product (Scheme 2).

This method can be used to prepare the phenazine derivative (**6**) from (−)-11-aminoapovincamine (**5**)[4] which can be also prepared from (**2**) by elimination of water (Scheme 3).

For the structure verification of compound (**2**) see the ^1H n.m.r. data given in Table 1.[5]

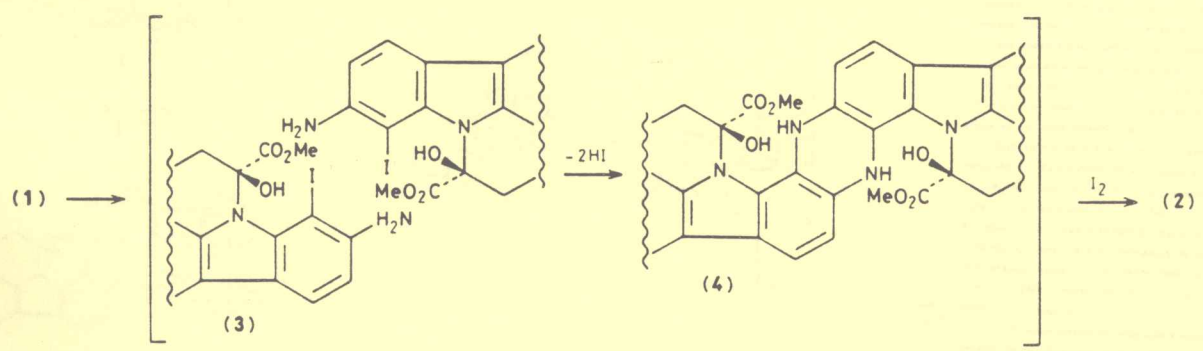


Scheme 1 Formation of the phenazine derivatives (**2**). The ^{13}C chemical shifts were measured at 100 MHz ($CDCl_3$; $SiMe_4$)

Table 1 ^1H Chemical shifts ($CDCl_3$; $SiMe_4$) and coupling constants (Hz) for compound (**2**), measured at 400 MHz

Proton	δ	^2J	Hz	^3J	Hz
3-H	3.98	5,5	[a]	5a,6a	[a]
5-$H_{e,a}$	3.30–3.50[a]	6,6	*ca.* 15.2	5a,6e	[a]
6-H_e	*ca.* 2.69[a]	15,15	14.3	5e,6a	[a]
6-H_a	*ca.* 3.08[a]	17,17	13.4	5e,6e	[a]
9-H	8.00	18,18	12.6	17a,18a	12.6
10-H	7.75	19,19	11.7	17a,18e	3.0
15-H_e	2.62	20,20	14.4	17e,18a	3.7
15-H_a	2.08			17e,18e	3.0
17-H_e	1.56	^4J		18a,19a	12.6
17-H_a	1.63	OH,15a	1.5	18a,19e	3.7
18-H_e	1.33	3,17e	[b]	18e,19a	3.0
18-H_a	1.72			18e,19e	3.0
19-H_e	2.58	^5J		9,10	10.2
19-H_a	2.35	3,6a	*ca.* 1.9		
20-H_x	2.27	3,6e	*ca.* 1.6		
20-H_y	1.49				
21-H_3	0.96				
OH	8.17				
OMe	3.72				

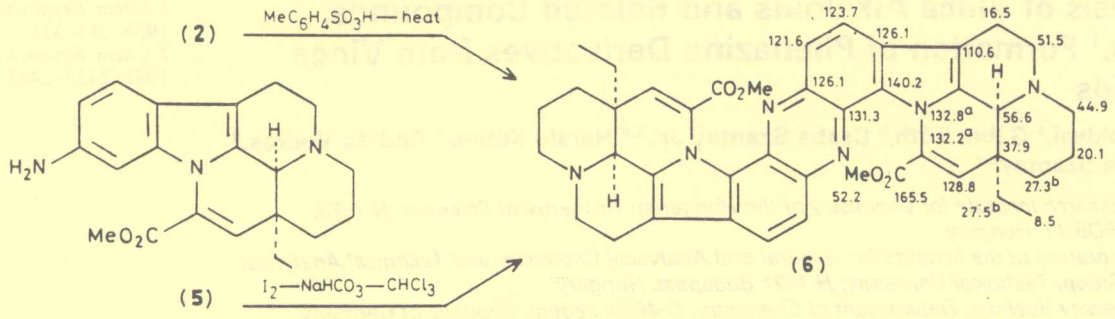
[a] Higher-order sub-spectrum. [b] Unresolved long-range coupling interaction which is detected in the COSY-45 contour plot, optimized for long-range couplings.



Scheme 2

We thank Dr. J. Tamás and Miss M. Mák for recording mass spectra, Dr. S. Holly for i.r. spectra, and Mrs K. Welker for technical assitance. The authors are grateful to the

* To receive any correspondence.



Scheme 3 Formation of the phenazine derivative (**6**). The ^{13}C chemical shifts measured at 25 MHz ($CDCl_3$; $SiMe_4$) are also depicted (a, b = tentative assignments)

Hungarian Academy of Sciences and the OTKA program for financial support. One of us (G. T.) thanks the A. v. Humboldt Stiftung for a fellowship and Prof. G. Snatzke for helpful discussions.

Techniques used: Mass spectrometry, i.r., ^1H and ^{13}C n.m.r. spectroscopy; two-dimensional ^1H–^1H and ^{13}C–^1H (COSY, COLOC) correlation maps; homo- and hetero-nuclear n.O.e. difference measurements

References: 16

Figure 1: ^{13}C–^1H Hetero-correlated contour plot for compound (**2**)

Figure 2: Heteronuclear n.O.e. difference spectra for compound (**2**)

Table II: Observed ^{13}C–^1H long-range correlation of quaternary carbons for compound (**2**)

Received, 12th October 1987; Paper E/8/00379C

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J.CHEM.RESEARCH (M), 1988, 2419 — 2427

ν_{max} ($CHBr_3$) 1695, 1605, 1598, 1580, 1250, 835 cm^{-1}. δ_H 0.16 (6H, s, $Si(CH_3)_2$), 0.78 (9H, s, $SiC(CH_3)_3$), 1.75 and 1.77 (6H, 2 x s, 2 x CH_3), 3.18 (1H, dd, J_1 = 8Hz, J_2 = 16Hz, 9a-H), 3.39 (1H, dd, J_1 = 16Hz, J_2 = 2Hz, CH_2OSi), 3.76 (1H, d, J = 8Hz, 4a-H), 3.82 (1H, dd, J_1 = 16Hz, J_2 = 2Hz, CH_2OSi), 3.88 (3H, s, OCH_3), 5.84 (1H, s, 2-, or 3-H), 6.85 (1H, s, 5-H), 6.88 (1H, dd, J_1 = 8Hz, J_2 = 2Hz, 7-H), 7.55 (1H, d, J = 8Hz, 8-H) (Found: C, 69.2; H, 8.0 $C_{23}H_{32}O_4Si$ requires C, 68.9; H, 8.05%). On increasing the polarity of the eluting solvents the other isomer was isolated, but it was always contaminated with the above compound.

3'-Bromo-5'-methoxy-2',3'-dihydrospiro-(1,3-dithiolane-2,1'-[1H]indene)

Boron trifluoride diethyl etherate (2 drops) was added to a stirred mixture of 3-bromo-5-methoxy-indanone (200mg, 0.8mmol) and 1,2-ethanedithiol (0.2cm³, 2.38mmol) in dry dichloromethane (5cm³) at 0°C under an atmosphere of dry nitrogen. After 1h the reaction mixture was diluted with dichloromethane (25cm³) and washed in turn with 5% aqueous sodium hydroxide and saturated brine, dried ($MgSO_4$), and evaporated under reduced pressure to yield the title compound as an orange oil (0.26g). (This product is quite pure but very unstable under conditions of column chromatography on silica). δ_H ($CDCl_3$) 3.20 (2H, m, 2-CH_2), 3.35 (4H, brs, 5-CH_2-CH_2-S), 3.70 (3H, s, -OCH_3), 5.30 (1H, t, J = 5Hz, 3-CHBr), 6.75 (2H, m, 4-H, 6-H), 7.40 (1H, d, J = 8Hz, 7-H).

2407 3-(1-Methylbutyl)pyridine (25)

n-Butyllithium in hexane (2cm³, 4.6mmol) was added dropwise to dry diisopropylamine (0.65cm³) in dry tetrahydrofuran (5cm³) protected by a nitrogen atmosphere. Hexamethylphosphoric triamide (0.8cm³) was added and the mixture was cooled to -10°C and treated with 3-ethylpyridine (0.5cm³) in tetrahydrofuran (5cm³) over a 5 minute period. After a further 30 minute, a solution of bromopropane (0.6cm³) in dry tetrahydrofuran (5cm³) was added and the reaction mixture allowed to warm to room temperature. It was then poured onto ice and 10% hydrochloric acid (35cm³), basified by the addition of solid potassium hydroxide, and extracted with diethyl ether (3 x 25cm³). The combined extracts were washed with water, brine then dried and evaporated under reduced pressure to give a yellow oil.

column chromatography of which eluting with methanol: ethyl acetate (1:99) afforded the title compound as a near colourless oil (315mg, 45%). ν_{max} (liquid) cm⁻¹ 1570. δ_H ($CDCl_3$) 0.85 (3H, d, J = 6Hz, CH_3), 1.0-1.7 (7H, brm, aliphatic protons), 2.60 (1H, m, J 6Hz, 2'-H), 7.0 (1H, m, 5-H), 7.35 (1H, m, 4-H), 8.28 (2H, brs, 2-H, 6-H). δ_C ($CDCl_3$), 13.98 (q, C-5'), 20.64 (t, C-6'), 21.94 (q, C-1''), 37.22 (d, C-2''), 40.36 (t, C-3''), 123.30 (d, C-5), 134.08 (d, C-4), 142.75 (s, C-3), 147.61 (d, C-6), 149.20 (d, C-2), m/z (%) 149 (M^+, 21), 106 (100) (Found (m/z): 149.1203 $C_{10}H_{15}N$ requires 149.1203).

2417 5'-Methoxy-2',3'-dihydro-spiro(1,3-dithiolane-2,1'-[1H]indene) (26)

Boron trifluoride diethyl etherate (0.2cm³) was added to 5-methoxyindanone (2g, 12mmol) and 1,2-ethanedithiol (2cm³) in dry dichloromethane (20cm³) maintained at 0°C under a nitrogen atmosphere. The mixture was allowed to warm to room temperature during 48h and then it was diluted with dichloromethane (50cm³) and washed with 5% aqueous sodium hydroxide (2 x 15cm³), brine (25cm³). After drying the solvents were removed and the residue chromatographed (ethyl acetate: petrol,1:4) to give the title compound as colourless prisms (2.6g, 89%), m.p. 57°C; ν_{max} ($CHCl_3$) cm^{-1} 1608, 1585, δ_H ($CDCl_3$) 2.68 (2H, t, J = 6Hz, 2-CH_2), 2.98 (2H, brt, J = 6Hz, 3-CH_2), 3.04, 3.46 (2 x 2H, 2 x d, CH_2CH_2S), 3.78 (3H, s, OCH_3), 6.72 (1H, s, 4-H), 6.80 (1H, dd, J_1 = 8Hz, J_2 = 2Hz, 6-H), 7.45 (1H, d, J = 8Hz, 7-H); m/z (%) 238 (M^+, 34), 210 (38), 178 (100), 165 (97) (Found m/z: 238.0477 $C_{12}H_{14}S_2O$ requires: 238.0485).

2407 2,3-Dihydro-7-methoxy-1H-1,6-dithiafluorene (27)

N-Bromosuccinimide (380mg) was added in three portions during 40min to a mixture of 5'-methoxy-2',3'-dihydrospiro(1,3-dithiolane-2,1'-[1H]indene) (500mg) and benzoyl peroxide (20mg) in carbontetrachloride (20cm³) at reflux. After 2h more, N-bromosuccinimide (100mg) was added and heating continued for 1h then succinimide which had formed was filtered off from the cooled reaction mixture and the filtrate washed with brine (5cm³), dried and evaporated to give a brown oil.

Column chromatography eluting with ethyl acetate: petrol (1:4) yielded a colourless crystalline solid (450mg), m.p. 83-85°C; δ_H ($CDCl_3$), 3.25 (4H, s, 2-H_2, 3-H_2), 3.40 (2H, s, 9-CH_2), 3.78 (3H, s, OCH_3), 6.78 (1H, dd, J_1 = 8Hz, J_2 = 2Hz, 6-H), 6.90 (1H, d, J = 2Hz, 8-H), 7.00 (1H, d, J = 8Hz, 5-H), δ_C ($CDCl_3$) 26.06, 27.2 (2 x t, C-2, C-3), 42.31 (t, C-9), 55.53 (q, OCH_3), 110.03, 111.49, 116.80 (3 x d, C-5, C-6, C-8), 123.01, 124.38 (2 x s, C-4a, C-9a), 137.12, 141.34, 157.54 (3 x s, C-4b, C-7, C-8a); m/z (%) 236 (M^+ 100), 208 (57), 164 (46) (Found: m/z): 236.0320 $C_{12}H_{12}OS_2$ requires: 236.0327).

This compound rapidly turns red in air and resinifies.

Paper E/8/00379C Received 12th October 1988

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Synthesis of Vinca Alkaloids and Related Compounds XXXIX[1]

Formation of Phenazine Derivatives from Vinca Alkaloids

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a/ On Leave from the Chemical Works of Gedeon Richter Ltd.

References: see frame 2440.

A unique formation of phenazine derivatives of some indole alkaloids has been discovered. Structural elucidation of the new compounds by NMR spectroscopy is discussed.

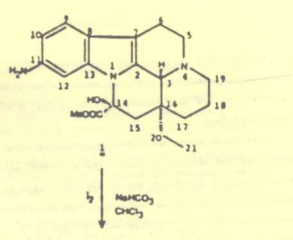
In the course of our studies aimed at finding structure - bioactivity relationships among Vinca alkaloid derivatives the iodination of (+)-11-amino vincamine (1)[2] was performed.

It is well documented that reactions of aromatic amines with iodine in alkaline medium yield, as a rule, o- and p-substituted derivatives. Thus in our case the formation of 10- or 12-iodo-11-amino vincamine was expected.

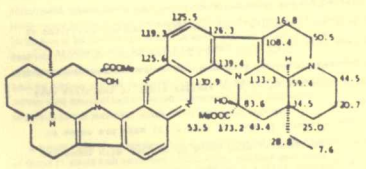
When 1 was treated with iodine in a mixture of chloroform and saturated aqueous $NaHCO_3$ at room temperature for 2 h, instead of the expected compound a red crystalline substance was obtained in 30 % yield. On the grounds of spectroscopic investigations the new compound proved to be the phenazine derivative 2, possessing a C_2 rotation axis in the centre of the pyrazine ring.

The sequence of events leading to 2 may be envisaged as follows. In the first step the iodo compound (3) is formed which affords subsequently by elimination of hydrogen iodide the dihydrophenazine derivative (4). The latter compound is then aromatised by iodine to the end product 2 (Scheme 2).

References: see frame 2440.

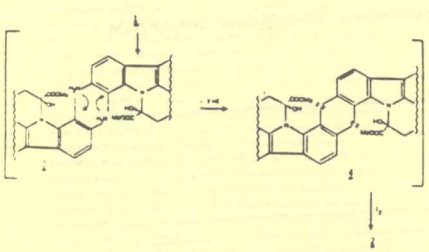


1a



2

Scheme 1. Formation of phenazine derivative 2. The ^{13}C chemical shifts measured at 100 MHz ($CDCl_3$, δ_{TMS} = 0.0 ppm).



Scheme 2.

To the best of our knowledge no such direct formation of phenazines through iodination of aromatic amines has been reported previously in the literature[3].

The special electronic effects prevailing over the benzene ring of vincamine are likely to be responsible for this unique reaction. These facilitate both iodination at C-12, and the subsequent nucleophilic attack by the amino group at the same carbon atom.

That such a delicate balance of electronic factors is required for fulfillment of the above reaction was supported by the fact that, while (+)-11-aminoapovincamine (5)[4] gave rise to the analogous phenazine derivative (6), (+)-11-amino-vincamone[2] which has a carbonyl group attached to the N_{ind}, thus diminishing its electron-donating effect, afforded no such product under similar conditions. Elimination of water from 2 yielded 6 revealing the relationship between the two compounds (Scheme 3).

(+)-9-Aminovincamine[2] was again unable to provide the corresponding phenazine derivative.

NMR Spectroscopy

The structure of compound 2 was elucidated by detailed ^1H (400 MHz) and ^{13}C (100 MHz) NMR investigations. Although the dimeric character of the molecule was clearly established by the MS data, this was not reflected in the number of

References: see frame 2440.

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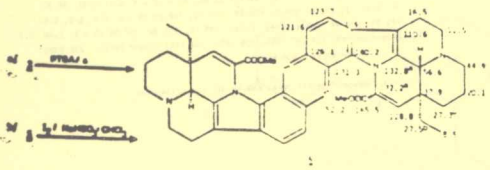


Scheme 3. Formation of the phenazine derivative 4. The ^{13}C chemical shifts measured at 25 MHz are also depleted. ($CDCl_3$, δ_{TMS} = 0.0 ppm; a,b = tentative assignments).

signals in the NMR spectra, which pointed to a symmetric arrangement of the two units. The presence of the J=10.2 Hz coupled AB doublets in the aromatic region of the ^1H NMR spectrum (δ 8.00 and 7.75 ppm) indicated that the substitution of the starting compound took place on C-12[5]. Furthermore, a comparison of the ^1H and ^{13}C NMR data with those of vincamine[6] revealed that other parts of the molecule remained intact, leading to the structure shown in Scheme 1.

The ^{13}C shifts in the aliphatic region are in accordance with those of vincamine[6] and thus allow straightforward assignments. These provided a good basis for assigning the aliphatic region of the ^1H NMR spectrum (Table I.), with the aid of 2D (two-dimensional) ^{13}C-^1H [7] (Fig. 1.) and ^1H-^1H (COSY-45)[8] correlation maps. The COSY-45 measurement was optimised for 2.5 Hz couplings, thus allowing the detection of long-range scalar correlations, such as ^5J ($J_{6_a,6_e}$)[9] and ^4J ($J_{3,17_e}$). For assigning H-9 and H-10, a homonuclear NOE-difference measurement was used: irradiation of H_{ax}-6 produced a 2.1 % intensity enhancement on the H-9 signal (δ 8.00) due to the close proximity of these protons, while no NOE was found on H-10 (δ 7.75). In this experiment NOE-s were also found on the geminal H_{eq}-6 signal (19 %) and on H_{ax}-19 (4 %), the latter being incident to the cis C/D ring fusion of the eburnane skeleton. It is worth mentioning that, upon irradiating H-9 with the aim of justifying its assignment in a reversed way (by exploiting the short interproton distance between H-9 and $H_{a,e}$-6), a significant NOE was found only on H-10, with none on H_{ax}-6 or H_{eq}-6, due to their many sources of relaxation[10].

References: see frame 2440 and 2441.

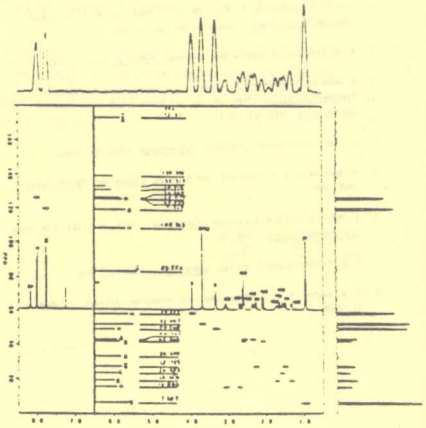
Table I. ^1H chemical shifts (δ_{TMS} = 0.00 ppm) and coupling constants (Hz) for compound 4, measured at 400 MHz in $CDCl_3$.

proton	δ	^2J	(Hz)	^3J	(Hz)
H-3	3.98	5,5	a	5a,6a	a
$H_{e,e}$-5	3.30-3.50[a]	6,6	-15.2	5a,6e	a
H_e-6	~2.69[a]	15,15	14.3	5e,6a	a
H_a-6	~3.08[a]	17,17	13.4	5e,6e	a
H-9	8.00	18,18	12.6	17a,18a	12.6
H-10	7.75	19,19	11.7	17a 18e	3.0
H_e-15	2.62	20,20	14.4	17e,18a	3.7
H_a-15	2.08			17e,18e	3.0
H_e-17	1.56	^4J		18a,19a	12.6
H_a-17	1.63	OH,15a	1.5	18a,19e	3.7
H_a-18	1.33	3,17e	b	18e,19a	3.0
H_a-18	1.72			18e,19e	3.0
H_e-19	2.58	^5J		9,10	10.2
H_a-19	2.35	3,6a	~1.9		
H_a-20	2.27	3,6e	~1.6		
H_y-20	1.49				
H_3-21	0.96				
OH	8.17				
OMe	3.72				

[a] higher order subspectrum

[b] unresolved long-range coupling interaction which is detected in the COSY-45 contour-plot, optimised for long-range couplings

Figure 1. The ^{13}C-^1H hetero correlated contour plot for compound 4, measured at 9.4 Tesla. Insets show the normal ^1H spectrum (horizontal) and the broad-band ^1H decoupled ^{13}C spectrum (vertical).



The high-field ^1H NMR spectrum of compound 4 also revealed some interesting details worthy of mention. Thus ^2J ($J_{19_a,19_e}$) has a characteristic small absolute value (11.7 Hz) owing to the antiperiplanar effect of the nitrogen lone pair on H_{ax}-19 [11]. Owing to the chiral structure, the $H_{x,y}$-20 methylene protons are diastereotopic. Their large chemical-shift difference ($\Delta\delta(H_{x,y})$ = 0.78 ppm), however, indicates that the populations of the possible conformations around the C-16 —— C-20 bond may be very different. As is found in other indole alkaloids, $\delta(H_{ax}$-6) is larger than $\delta(H_{eq}$-6), owing to the anisotropic effect of the condensed aromatic system[12], and possibly also to the Van der Waals interaction[13] between H_{ax}-6 and H_{ax}-19. A similar "reversed" chemical shift relationship is found concerning the axial and equatorial geminal protons on C-17 and C-18. In both cases, the phenomenon can be explained by the presence of strong Vga der Waals effects on the appropriate axial protons arising from the C-14 OH in the former and from C-20 H_y in the latter case. Note that the OH signal shows a 1.5 Hz long-range coupling to H_{ax}-15, reflecting the presence of a preferred conformation for the OH group in which the OH proton is oriented towards the pyrazine ring, thus implementing a "W" pathway (which is a favoured arrangement for ^4J (H,H) coupling) between the OH and H_{ax}-15 proton. The OH proton is also significantly deshielded (δ 8.17, i.e. 3.5 ppm downfield of its value in vincamine[6]); this can be attributed to the close proximity of the condensed aromatic system, particularly the pyrazine ring.

References: see frame 2440 and 2441.

The assignment of H-9 and H-10 allowed the unambiguous identification of the C-9 and C-10 signals by considering the corresponding correlations in the hetero-correlated 2D spectrum (Fig.1).

The question of assigning the C-2, C-8, C-13, C-12 and C-11 quaternary signals was partly solved through recording a COLOC spectrum[14] which showed long-range ^{13}C-^1H coupling correlations (the experiment was optimised for 6 Hz couplings - see Table II). However, from the fact that both C-8 and C-12 correlate with H-10 only, and C-11 and C-13 correlate with H-9 only (through the corresponding ^3J (C,H) couplings), it is obvious that the differentiation of these signals needed further experiments.

Heteronuclear NOE difference spectra were therefore recorded while irradiating the H-10 or H-9 signal. This experiment exploits the fact that low-power irradiation of suitable narrow ^1H peaks results in NOE enhancement in the neighbouring quaternary carbons, positioned two bonds from the irradiated proton[15]. The corresponding intensity enhancements (on C-11 and on C-8, respectively -see Fig.2, spectra b and c) allowed the assignment of the above-mentioned quaternary carbons. Spectrum d of Fig.2 was achieved with the same pulse-programming[15] as for spectra b and c but, instead of moving the low-power irradiation frequency (which was first set on H-9) into a neutral part of the ^1H region in the reference (subtracted) spectrum, it was switched onto H-10. An alternation of the irradiation between H-9 and H-10

References: see frame 2441.

Table II. Observed ^{13}C-^1H long-range correlation of quaternary carbons for compound 4.

	^2J	^3J
C-2	H-3	H_e-6
C-7	H_a-6,H_e-6	H-3
C-8		H-10
C-11		H-9
C-12		H-10
C-13		H-9
C-14	H_e-15, OH	
C-16	H_a-15, H_e-15, H-3	H_a-18
C=O		H_a-15, OMe, OH

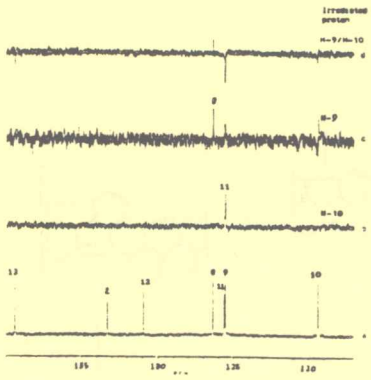


Figure 2. Heteronuclear NOE difference spectra for compound 4.
a./ Part of the low field region of the broad-band ^1H decoupled ^{13}C spectrum.
b./, c./ and d./: spectra gained when irradiating H-10, H-9 and H-10 or H-9 -see text.

thus resulted in a positive and a negative peak in the difference spectrum due to the appropriate NOE enhancements, thus providing the same information as spectra b and c, but in one experiment.

It is interesting that the employment of direct-assignment methods for the identification of the aromatic carbon signals was particularly important due to the complexity of the conjugated system. (In such systems large deviations may often occur between calculated and measured chemical shifts). Indeed, a comparison of the above assignments for 4 with those calculated from simple additivity constants (derived from the ^{13}C data for phenazine[16] and benzene[16]) showed deviations of the kind that would have completely misled the aromatic ^{13}C assignments if use of the latter approach had been attempted. Careful handling of data in similar cases is therefore very important.

For compound 4, the ^{13}C shifts (25 MHz) are shown in Scheme 3. Assignments were based by analogy with those for 4. ^1H chemical shifts (100 MHz) are given in the Experimental section. Interestingly, the OMe signal in the ^1H spectrum at room temperature was broad, being buried among the complex overlapping skeletal signals in an unidentifiable manner. At 50 °C, however, the OMe signal appeared as a sharp singlet (δ 3.58). The phenomenon can be explained by the close proximity of the pyrazine-nitrogen lone pair which hinders free rotation around the C-16 —— COO bond.

References: see frame 2441.

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Experimental

The UV absorption spectra were recorded on a UV Specord UV-VIS spectrometer. IR spectra were recorded on NIC 7199 and Specord IR 75 spectrometers using KBr pellets. Mass spectra were taken on an AEI-MS-902 (70 eV, direct insertion) mass spectrometer. M.p.'s are uncorrected.
All the NMR spectra were recorded in the FFT mode, with internal deuterium lock at ambient temperature (298 K), in $CDCl_3$ using TMS as internal standard. The ^1H and ^{13}C NMR measurements for compound 2 were performed at 400 and 100 MHz, respectively, on a Bruker AM-400, while those for compound 6 were at 100 and 25 MHz, respectively, on a Jeol FX-100 spectrometer. The ^1H chemical shifts and coupling constants were calculated as first-order spectra at 400 MHz. NOE-difference and two-dimensional experiments were recorded by using the Bruker software package. For homonuclear NOE measurements a delay time of 3 s was used, while for heteronuclear NOE measurements the value was 25 s.

Dimethyl(11R,12aR,18cR,23S,24aR,24bR)-(12a,24a-diethyl-11,23-dihydroxy-1,2,3,5,6,11,12,12a,13,14,15,17,18,18c,23,24,24a,24b-octadecahydro-9H-indolizino[2',3':3a',3':1,8a,8,7]indolizino[1:2-a][1,4]-benzodiazonine-11,23-dicarbonyl)ate (2)

2425

(+)-11-Aminovincamine (1, 3.69 g, 10 mmol) was dissolved in a mixture of 150 ml chloroform and 30 ml saturated $NaHCO_3$ solution. Iodine (5.05 g, 20 mmol) was added and the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered and the layers of the filtrate were separated. The organic phase was washed with a sodium thiosulfate solution (10 %, 2x25 ml) then with water (4x25 ml), dried (Na_2SO_4), filtered and evaporated in vacuo. The residue (2.1 g) was dissolved in hot methanol (50 ml), cleared with active carbon, filtered and the filtrate was kept in refrigerator overnight. The obtained red crystals were filtered off, washed with methanol (2x4 ml), dried to yield 2 (1.1 g, 30 %); m.p. over 360 °C (decomp.); Found: C, 68.59; H, 6.57; N, 11.07. $C_{42}H_{48}N_6O_6$ requires C, 68.83; H, 6.60; N, 11.47 %; ν_{max} (KBr) 3 400, 1 750, 1 565, 1 540, 1 100 cm^{-1}; λ_{max} (EtOH) 204, 272, 323, 443, 509 nm; m/z 732 (M^+, 32 %), 673 (M-59, 100), 665 (M-87, 32), 614 (8), 613 (8), 597 (4), 585 (4), 489 (5), 461 (5), 366 (M^{2+}, 18); for NMR data, see Scheme 1 and Table 1.

Dimethyl(12aR,18cR,24aR,24bR)-(12a,24a-diethyl-1,2,3,5,6,12a,13,14,15,17,18,18c,24a,24b-tetradecahydro-9H-indolizino[2',3':3a',3':1,8a,8,7]indolizino[1:2-a][1,4]benzodiazonine-11,23-dicarbonyl)ate (6)

2426

a./ A mixture containing 2 (183 mg, 0.25 mmol) and p-toluenesulphonic acid monohydrate (0.6 g, 3.1 mmol) in benzene (10 ml) was refluxed by using a water-trapping device for 10 h then cooled. After adding 5 ml of water, the pH was adjusted to 8 by using concentrated aqueous ammonium hydroxide solution. After extraction, the organic layer was washed with water (3x15 ml), dried (Na_2SO_4), and filtered and the filtrate was evaporated to dryness in vacuo. The residue was crystallized from acetone (2 ml) to yield 6 (120 mg, 72 %).

b/ 6 was prepared according to the above procedure for 2.
M.p. over 360 °C (decomp.); (Found: C, 72.22; H, 6.29; N,13.98. $C_{42}H_{44}N_6O_4$ requires C, 72.39; H, 6.36; N, 12.06 %); ν_{max} (KBr) 1 720, 1 650, 1 430, 1 420 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.05 (3 H, s, 21-Me), 4.19 (1 H, s, 3-H), 3.38 (broad, -CHN; sharp only upon heating sample - see: text), 6.29 (1 H, s, 15-H), 7.87 (1 H, s, 2 9 Hz, 9-H), 7.79 (1 H, d, 10-H), - 0.80- ~ 3.7 (17H, m, skeletal + 20-CH_2); for ^{13}C NMR data, see Scheme 3.

Acknowledgements

The authors wish to thank Dr. J. Tamás and Miss, M. Nán for mass spectra and Dr. S. Holly for i.r. spectra.
They are grateful to the Hungarian Academy of Sciences for financial support.
One of us (G.T.) thanks the A. v. Humboldt Stiftung for a fellowship (Ruhr University, Bochum) and to Prof. G. Snatzke for helpful discussions.
Special thanks are due to Mrs. E. Wajker for technical assistance.

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Paper E/B/020941 Received 25th May 1988

Absolute Rate Data for the Reaction of Atomic Germanium, Ge($4p^2$ ^3P_J), with Halogenated Olefins and Aromatic Compounds by Time-Resolved Atomic Resonance Absorption Spectroscopy

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Summary

We present a kinetic study of the collisional behaviour of atomic germanium with various halogenated olefins and aromatic compounds. Ge($4p^2$ ^3P_J), generated by the repetative pulsed irradiation of $Ge(CH_3)_4$ in a slow flow system, kinetically equivalent to a static system, was monitored by time-resolved atomic resonance absorption spectroscopy with signal averaging at λ = 259.3 nm ($Ge(5s^2\,^3P_2)$ ⟶ $Ge(4p^2(^3P_J))$) following Boltzmann conservation within the ^3P_J ground state spin-orbit manifold. Absolute second-order rate constants are reported for the collision partners. CH_2CF_2, $CHCl_2CCl_2$, C_2Cl_4, $CF_3CH=CH_2$, C_6H_5, C_6H_5F, C_6F_6 and C_6F_5-CF_3 indicating reaction proceeding at close to unit collision efficiency in all cases with atomic germanium. These data are considered within the context of previous measurements of rate constants for reactions of Ge($4p^2$ ^3P_J) with hydrocarbon olefins and acetylenes, with analogous data for Si($3p^2$ ^3P_J) and also within the context of rate data for ground state atomic reactions of Group IV atoms with unsaturated organic molecules in general.

2440 2441 2442

INTRODUCTION

Characterisation of absolute rate data for the collisional removal of ground state atoms by unsaturated hydrocarbons such as olefins and acetylenes is an established area of gas phase kinetics in general. It is, however, only recently that such kinetic investigations for Group IV atoms, particularly the lighter atoms, have been carried out by direct spectroscopic monitoring in the time-resolved mode. Husain et al.[1,2] have reported third-order rate data for the removal of Pb(6^3P_0) and Si(3^3P_0) with C_2H_4 and using time-resolved atomic resonance absorption spectroscopy in the single-shot mode. The present authors, following the earlier kinetic measurements on the reaction between Si(3^3P_J) + C_2H_4 by Husain and Norris,[3] have reported absolute second-order rate constants for the reactions of Si(3^3P_J)[4] and Ge(4^3P_J)[5] Boltzmann-ised within the ^3P_J spin-orbit state manifold, with a wide range of hydrocarbon olefins using time-resolved atomic resonance absorption spectroscopy following repetative pulsed irradiation and signal averaging. To the best of our knowledge, to date no absolute rate measurement has been reported for the reaction between Cl(2^2P_J) + C_2H_4 by direct monitoring of the atom though Martinotti et al.[6] have reported an upper limit for reaction in a flow discharge system with measurement of the carbon atom concentration by its conversion with excess molecular oxygen to carbon monoxide, measured by gas chromatography.

A similar range of measurements have been reported for the reaction of Group IV atoms with acetylenes. Third-order rate data have been presented for the reactions of Pb(6^3P_0) and Si(3^3P_0) + C_2H_2 in the single-shot mode.[1,2] Second-order rate measurements in this mode using atomic resonance absorption spectroscopy following flash photolysis have been reported for the reactions between Ge(4^3P_J) + C_2H_2 and C_2H_6.[7] As before, we have reported a wide range of absolute second-order rate constants for the reactions of Si(3^3P_J)[8,9] and Ge(4^3P_J)[10] with acetylenes using signal averaging techniques. Such kinetic comparisons of the collisional behaviour of Si and Ge have been carried out against the broad background of measurements of products resulting from the collision of ^3P_J, generated by nuclear recoil, with unsaturated organic targets.[11-15]

As with C + C_2H_4, Martinotti et al.[6] report a similar second-order upper limit for the reaction rate constant for Cl(2^2P_J) + C_2H_2 using their flow discharge method. Clearly, absolute rate constants for reactions of Cl(2^2P_J) with these simple hydrocarbon molecules await direct direct characterisation by time-resolved atomic resonance absorption spectroscopy in the vacuum ultra-violet, especially in view of the detection of isotope-labelled atoms from the reaction of ^{13}C with C_2H_4 by Wolfgang et al.[16] In the paper we describe measurements of absolute second-order rate constants for reactions of Ge(4^3P_J) with a range of halogenated unsaturated organic molecules, namely, CH_2CF_2, $CHCl_2CCl_2$, C_2Cl_4, $CF_3CH=CH_2$, C_6H_5, C_6H_5F, C_6F_6 and C_6F_5-CF_3. Ge(4^3P_J) was generated by repetative pulsed irradiation of $Ge(CH_3)_4$ in the presence of excess helium buffer gas in a slow flow system. Kinetically equivalent to a static system, and monitored by time-resolved atomic resonance absorption spectroscopy using signal averaging.[3,10] This procedure may be contrasted with the single-shot mode measurements on Ge($4^3P_{0,2}$) reported hitherto.[7,17-19] The measurements were carried out on time scales by which spin-orbit relaxation had taken place within Ge(4^3P_J) as evidenced by the equality in the kinetic decay coefficients that had been demonstrated from observations on individual spin-orbit components including such measurements as a function of temperature.[7,18] Thus the rate data are attributed to Ge(4^3P_J). Ge(4^3P_1) was chosen for monitoring for reasons of experimental sensitivity (see experimental). Measurements were also carried out on time scales by which the higher lying states Ge($4p^2$($^1D_2$)) and Ge($4p^2$($^1S_0$)) respectively, 0.883 and 2.09 eV above the $4p^2$ ^3P_J ground state,[20] initially generated photochemically in the present type of system (see experimental), had been removed. The resulting rate data for Ge(4^3P_J) are compared with the second-order rate data that we have reported for the analogous reactions for Si(3^3P_J) using signal averaging techniques.[21]

EXPERIMENTAL

The experimental arrangement for monitoring Ge(4^3P_J) by time-resolved atomic resonance absorption spectroscopy in the repetitive mode at λ = 259.3 nm ($Ge(5s^2\,^3P_2)$ ⟶ $Ge(4p^2(^3P_1))$, $gA = 11 \pm 10^8$ s^{-1} 22) subsequent to pulsed irradiation essentially follows the procedure described hitherto[3,10] based on the combination of earlier aspects employed for monitoring atomic germanium in the single-shot mode[7,17-19] with those described initially for Si(3^3P_J) using signal averaging techniques.[3,8,9] Thus the transient atom was generated by the repetitive pulsed irradiation (E = 160 ± 05 J/(2) of low concentrations of Ge(CH_3)$_4$ in the presence of excess helium buffer gas (He) (Ge(CH_3)$_4$] ca 10^{14}]) through high purity Spectrosil quartz (i.d. = ca 16.5 mm), in a coaxial lamp and vessel assembly constituting part of a slow flow system. Kinetically equivalent to a static system. The spectroscopic source for the resonance transition was a microwave-powered flow lamp (incident power = ca 92 W EMI microwave generator type T1001) with a Fehsenfeld cavity[22] and a double stub tuner (Narda, U.S.A.) employing a mixture of $GeCl_4$ + He in the flow (2% $GeCl_4$ in He, P_{total} = ca 1 Torr (1 Torr = 133.3 Nm^{-2})). The atomic line was isolated in an optics with a one metre concave grating monochromator (Hilger and Watts) and monitored photoelectrically (EMI 9 pm tube type 9816 QB). This high gain photomultiplier tube was employed in the delayed mode to eliminate the electronic effects of scattered light from the pulsed irradiation source, in contrast to the earlier use with this tube of pre-trigger photomultiplier gating, for the original resonance absorption measurements on Si(3^3P_J) described by Husain and Norris.[3,4,21] The resulting photoelectric signals at λ = 259.3 nm, representing resonance absorption by Ge(4^3P_J), were amplified without distortion using a current-to-voltage converter employing a fast-settling operational amplifier,[23] captured, stored and digitised on a transient recorder (Data Laboratories DL 920, 2048 digitised data points), which was, in turn, interfaced to a signal averager (Data Laboratories, DL 4000). The

References: see frames 2458-2460.

References: see frames 2458-2460.

References: see frames 2458-2460.

2443 2444

Az olvashatóság érdekében az előző publikáció "miniprint" szedésű részét ismételten megadom az eredeti kézirat formájában.

Synthesis of Vinca Alkaloids and Related Compounds XXXIX[1]

Formation of Phenazine Derivatives from Vinca Alkaloids

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A unique formation of phenazine derivatives of some indole alkaloids has been discovered. Structural elucidation of the new compounds by NMR spectroscopy is discussed.

In the course of our studies aimed at finding structure - bioactivity relationships among Vinca alkaloid derivatives the iodination of (+)-11-amino vincamine (1)[2] was performed.

It is well documented that reactions of aromatic amines with iodine in alkaline medium yield, as a rule, o- and p-substituted derivatives. Thus in our case the formation of 10- or 12-iodo-11-amino vincamine was expected.

When 1 was treated with iodine in a mixture of chloroform and saturated aqueous $NaHCO_3$ at room temperature for 2 h, instead of the expected compound a red crystalline substance was obtained in 30 % yield. On the grounds of spectroscopic investigations the new compound proved to be the phenazine derivative 2, possessing a C_2 rotation axis in the centre of the pyrazine ring.

The sequence of events leading to 2 may be envisaged as follows. In the first step the iodo compound (3) is formed which affords subsequently by elimination of hydrogen iodide the dihydrophenazine derivative (4). The latter compound is then aromatized by iodine to the end product 2 (Scheme 2).

To the best of our knowledge no such direct formation of phenazines through iodination of aromatic amines has been reported previously in the literature[3].

The special electronic effects prevailing over the benzene ring of vincamine are likely to be responsible for this unique reaction. These facilitate both iodination at C-12, and the subsequent nucleophilic attack by the amino group at the same carbon atom.

That such a delicate balance of electronic factors is required for fulfillment of the above reaction was supported by the fact that, while (-)-11-aminoapovincamine (5)[4] gave rise to the analogous phenazine derivative (6), (+)-11-amino-vincamone[2] which has a carbonyl group attached to the N_{ind}, thus diminishing its electron-donating effect, afforded no such product under similar conditions. Elimination of water from 2 yielded 6 revealing the relationship between the two compounds (Scheme 3).

(+)-9-Aminovincamine[2] was again unable to provide the corresponding phenazine derivative.

NMR Spectroscopy

The structure of compound 2 was elucidated by detailed ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR investigations. Although the dimeric character of the molecule was clearly established by the MS data, this was not reflected in the number of

signals in the NMR spectra, which pointed to a symmetric arrangement of the two units. The presence of the J=10.2 Hz coupled AB doublets in the aromatic region of the ^{1}H NMR spectrum (δ 8.00 and 7.75 ppm) indicated that the substitution of the starting compound took place on C-12[5]. Furthermore, a comparison of the ^{1}H and ^{13}C NMR data with those of vincamine[6] revealed that other parts of the molecule remained intact, leading to the structure shown in Scheme 1.

The ^{13}C shifts in the aliphatic region are in accordance with those of vincamine[6] and thus allow staightforward assignments. These provided a good basis for assigning the aliphatic region of the ^{1}H NMR spectrum (Table I.), with the aid of 2D (two-dimensional) ^{13}C-^{1}H [7] (Fig. 1.) and ^{1}H-^{1}H (COSY-45)[8] correlation maps. The COSY-45 measurement was optimized for 2.5 Hz couplings, thus allowing the detection of long-range scalar correlations, such as ^{5}J $(3,6_{a,e})$[9] and ^{4}J $(3,17_{e})$. For assigning H-9 and H-10, a homonuclear NOE-difference measurement was used: irradiation of H_{ax}-6 produced a 2.1 % intensity enhancement on the H-9 signal (δ 8.00) due to the close proximity of these protons, while no NOE was found on H-10 (δ 7.75). In this experiment NOE-s were also found on the geminal H_{eq}-6 signal (19 %) and on H_{ax}-19 (4 %), the latter being incident to the <u>cis</u> C/D ring fusion of the eburnane skeleton. It is worth mentioning that, upon irradiating H-9 with the aim of justifying its assignment in a reversed way (by exploiting the short interproton distance between H-9 and $H_{a,e}$-6), a significant NOE was found only on H-10, with none on H_{ax}-6 or H_{eq}-6, due to their many sources of relaxation[10].

The high-field ^1H NMR spectrum of compound 2 also revealed some interesting details worthy of mention. Thus ^2J (19_a, 19_e) has a characteristic small absolute value (11.7 Hz) owing to the antiperiplanar effect of the nitrogen lone pair on H_{ax}-19 [11]. Owing to the chiral structure, the $H_{x,y}$-20 methylene protons are diastereotopic. Their large chemical-shift difference [$\Delta\delta(H_{x,y}) = 0.78$ ppm], however, indicates that the populations of the possible conformations around the C-16 —— C-20 bond may be very different. As is found in other indole alkaloids, $\delta(H_{ax}$-6) is larger than $\delta(H_{eq}$-6), owing to the anisotropic effect of the condensed aromatic system[12], and possibly also to the Van der Waals interaction[13] between H_{ax}-6 and H_{ax}-19. A similar "reversed" chemical shift relationship is found concerning the axial and equatorial geminal protons on C-17 and C-18. In both cases, the phenomenon can be explained by the presence of strong Van der Waals effects on the appropriate axial protons arising from the C-14 OH in the former and from C-20 H_2 in the latter case. Note that the OH signal shows a 1.5 Hz long-range coupling to H_{ax}-15, reflecting the presence of a preferred conformation for the OH group in which the OH proton is oriented towards the pyrazine ring, thus implementing a "W" pathway (which is a favoured arrangement for ^4J (H,H) coupling) between the OH and H_{ax}-15 proton. The OH proton is also significantly deshielded (δ 8.17, i.e. 3.5 ppm downfield of its value in vincamine[6]): this can be attributed to the close proximity of the condensed aromatic system, particularly the pyrazine ring.

The assignment of H-9 and H-10 allowed the unambigous identification of the C-9 and C-10 signals by considering the corresponding correlations in the hetero-correlated 2D spectrum (Fig.1).

The question of assigning the C-2, C-8, C-13, C-12 and C-11 quaternary signals was partly solved through recording a COLOC spectrum[14] which showed long-range ^{13}C-^{1}H coupling correlations (the experiment was optimized for 6 Hz couplings - see Table II). However, from the fact that both C-8 and C-12 correlate with H-10 only, and C-11 and C-13 correlate with H-9 only (through the corresponding ^{3}J (C,H) couplings), it is obvious that the differentiation of these signals needed further experiments.

Heteronuclear NOE difference spectra were therefore recorded while irradiating the H-10 or H-9 signal. This experiment exploits the fact that low-power irradiation of suitable narrow ^{1}H peaks results in NOE enhancement in the neighbouring quaternary carbons, positioned two bonds from the irradiated proton[15]. The corresponding intensity enhancements (on C-11 and on C-8, respectively -see Fig.2, spectra b and c) allowed the assignment of the above-mentioned quaternary carbons. Spectrum d of Fig.2 was achieved with the same pulse-programming[15] as for spectra b and c but, instead of moving the low-power irradiation frequency (which was first set on H-9) into a neutral part of the ^{1}H region in the reference (substracted) spectrum, it was switched onto H-10. An alternation of the irradiation between H-9 and H-10

thus resulted in a positive and a negative peak in the difference spectrum due to the appropriate NOE enhancements, thus providing the same information as spectra b and c, but in one experiment.

It is interesting that the employment of direct-assignment methods for the identification of the aromatic carbon signals was particularly important due to the complexity of the conjugated system. (In such systems large deviations may often occur between calculated and measured chemical shifts). Indeed, a comparison of the above assignments for 2 with those calculated from simple additivity constants (derived from the ^{13}C data for phenazine[16] and benzene[16]) showed deviations of the kind that would have completely misled the aromatic ^{13}C assignments if use of the latter approach had been attempted. Careful handling of data in similar cases is therefore very important.

For compound 6, the ^{13}C shifts (25 MHz) are shown in Scheme 3 (assignments were based by analogy with those for 2). ^{1}H chemical shifts (100 MHz) are given in the Experimental section. Interestingly, the OMe signal in the ^{1}H spectrum at room temperature was broad, being buried among the complex overlapping skeletal signals in an unidentifiable manner. At 50 ^{o}C, however, the OMe signal appeared as a sharp singlet (δ 3.58). The phenomenon can be explained by the close proximity of the pyrazine-nitrogen lone pair which hinders free rotation around the C-14 —— COO bond.

Experimental

The UV absorption spectra were recorded on a UV Specord UV-VIS spectrometer. IR spectra were recorded on NIC 7199 and Specord, IR 75 spectrometers using KBr pellets. Mass spectra were taken on an AEI-MS-902 (70 eV, direct insertion) mass spectrometer. M.p.'s are uncorrected.
All the NMR spectra were recorded in the PFT mode, with internal deuterium lock at ambient temperature (298 K), in $CDCl_3$ using TMS as internal standard. The ^1H and ^{13}C NMR measurements for compound 2 were performed at 400 and 100 MHz, respectively, on a Bruker AM-400, while those for compound 6 were at 100 and 25 MHz, respectively, on a Jeol FX-100 spectrometer. The ^1H chemical shifts and coupling constants were calculated as first-order spectra at 400 MHz. NOE-difference and two-dimensional experiments were recorded by using the Bruker software package. For homonuclear NOE measurements a delay time of 3 s was used, while for heteronuclear NOE measurements the value was 25 s.

Dimethyl(11S,12aS,18cR,23S,24aS,24bR)-(12a,24a-diethyl-11,23-dihydroxy-1,2,3,5,6,11,12,12a,13,14,15,17,18,18c,23,24,24a,24b-octadecahydrobis-{quinolizino[2',1',9a',9':1,8a,8,7]indolizino}[3,2-a][3,2-h]phenazine-11,23-dicarboxylate)-(2)

(+)-11-Aminovincamine (1, 3.69 g, 10 mmol) was dissolved in a mixture of 150 ml chloroform and 30 ml saturated $NaHCO_3$

solution. Iodine (5.05 g, 20 mmol) was added and the mixture was stirred at room temperature for 2 h. The raction mixture was filtered and the layers of the filtrate were separated. The organic phase was washed with a sodium thiosulfate solution (10 %, 2x25 ml) then with water (4x25 ml), dried (Na_2SO_4), filtered and evaporated in vacuo. The residue (2.1 g) was dissolved in hot methanol (50 ml), cleared with active carbon, filtered and the filtrate was kept in refrigerator overnight. The obtained red crystals were filtered off, washed with methanol (2x4 ml), dried to yield 2 (1.1 g, 30 %); m.p. over 360 °C (decomp); Found: C, 68.59; H, 6.57; N, 11.07, $C_{42}H_{48}N_6O_6$ requires C, 68.83; H, 6.60; N, 11.47 % ; ν_{max} (KBr) 3 400, 1 750, 1 565, 1 540, 1 100 cm^{-1}; λ_{max} (EtOH) 204, 272, 323, 443, 509 nm; m/z 732 (M^+, 32 %), 673 (M-59, 100), 645 (M-87, 32), 614 (8), 613 (8), 597 (4), 585 (4), 489 (5), 461 (5), 366 (M^{2+}, 18); for NMR data, see Scheme 1 and Table I.

Dimethyl(12aS,18cR,24aS,24bR)(12a,24a-diethyl-1,2,3,5,6,12a,13,14,15,17,18,18c,24a,24b-tetradecahydrobis{quinolizino[2',1',9a':1,8a,8,7]indolizino}[3,2-a][3,2-h]phenazine-11,23-dicarboxylate (6)

a./ A mixture containing 2 (183 mg, 0.25 mmol) and p-toluenesulphonic acid monohydrate (0.6 g, 3.1 mmol) in benzene (10 ml) was refluxed by using a water-trapping device for 10 h then cooled. After adding 5 ml of water, the pH was adjusted to 8 by using concentrated aqueous ammonium hydroxide solution. After extraction, the organic layer was washed with water

(3x15 ml), dried (Na_2SO_4), and filtered and the filtrate was evaporated to dryness in vacuo. The residue was crystallized from acetone (2 ml) to yield 6 (120 mg, 72 %).

b/ 6 was prepared according to the above procedure for 2.

M.p. over 360 °C (decomp); (Found: C, 72.22; H, 6.29; N,11.98. $C_{42}H_{44}N_6O_4$ requires C, 72.39; H, 6.36; N, 12.06 %); ν_{max} (KBr) 1 720, 1 650, 1 430, 1 420 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.05 (3 H, s, 21-Me), 4.19 (1 H, s, 3-H), 3.38 (broad, -OMe; sharp only upon heating sample - see: text), 6.29 (1 H, s, 15-H), 7.87 (1 H, s, J 9 Hz, 9-H), 7.79 (1 H, d, 10-H), ~ 0.80- ~ 3.7 (12H, m, skeletal + 20-CH_2); for ^{13}C NMR data, see Scheme 3.

Acknowledgements

The authors wish to thank Dr. J. Tamás and Miss. M. Mák for mass spectra and Dr. S. Holly for i.r. spectra.
They are grateful to the Hungarian Academy of Sciences for financial support.
One of us (G.T.) thanks the A. v. Humboldt Stiftung for a fellowship (Ruhr University, Bochum) and to Prof. G. Snatzke for helpful discussions.
Special thanks are due to Mrs. K. Welker for technical assistanc

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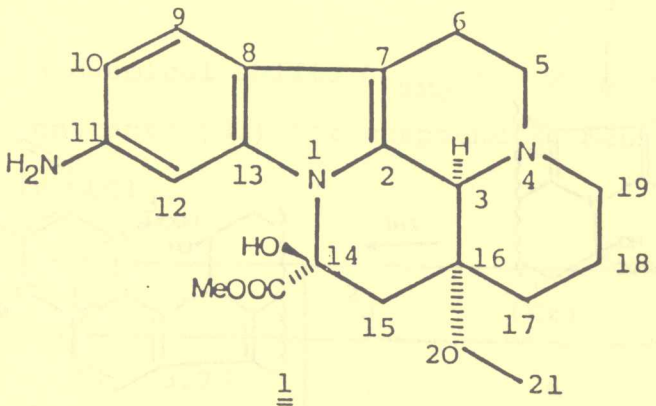
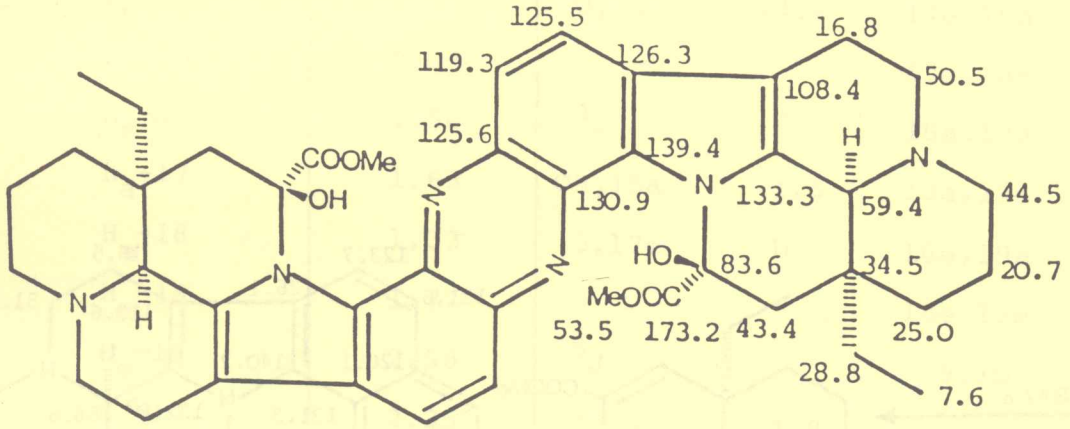


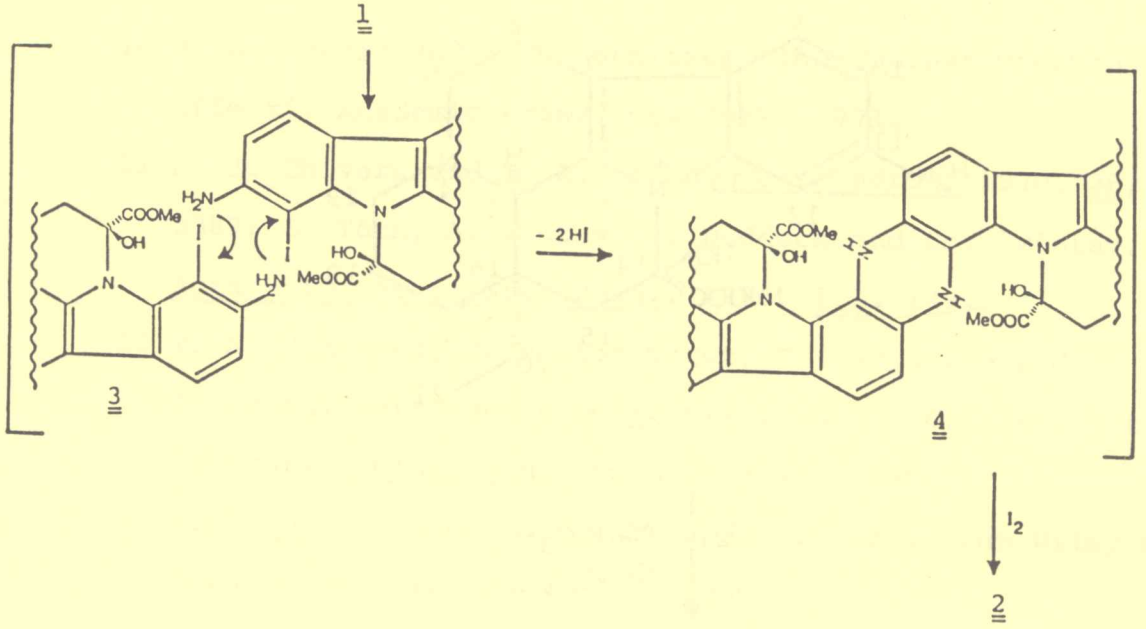
1

I_2 | $NaHCO_3$: $CHCl_3$

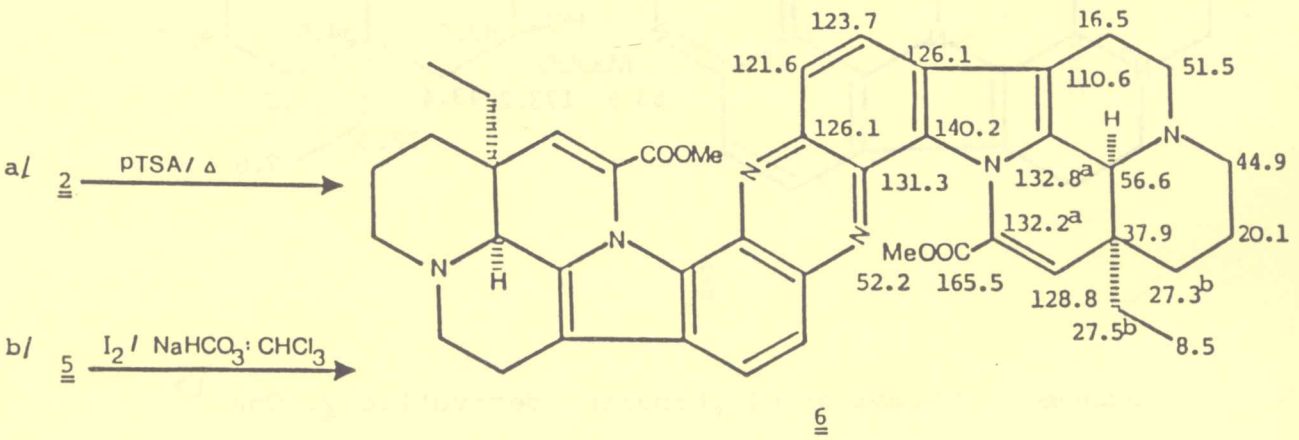


2

Scheme 1. Formation of phenazine derivative 2. The ^{13}C chemical shifts measured at 100 MHz ($CDCl_3$, δ_{TMS} = 0.0 ppm).



Scheme 2.



Scheme 3. Formation of the phenazine derivative 6. The ^{13}C chemical shifts measured at 25 MHz are also depicted. ($CDCl_3$, δ_{TMS} = 0.0 ppm; a,b = tentative assignments).

Table I. ^1H chemical shifts (δ_{TMS} = 0.00 ppm) and coupling constants (Hz) for compound 2, measured at 400 MHz in $CDCl_3$.

proton	δ	^2J	(Hz)	^3J	(Hz)
H-3	3.98	5,5	a	5a,6a	a
$H_{e,a}$-5	3.30-3.50[a]	6,6	~15.2	5a,6e	a
H_e-6	~2.69[a]	15,15	14.3	5e,6a	a
H_a-6	~3.08[a]	17,17	13.4	5e,6e	a
H-9	8.00	18,18	12.6	17a,18a	12.6
H-10	7.75	19,19	11.7	17a,18e	3.0
H_e-15	2.62	20,20	14.4	17e,18a	3.7
H_a-15	2.08			17e,18e	3.0
H_e-17	1.56	^4J		18a,19a	12.6
H_a-17	1.63	OH,15a	1.5	18a,19e	3.7
H_e-18	1.33	3,17e	b	18e,19a	3.0
H_a-18	1.72			18e,19e	3.0
H_e-19	2.58	^5J		9,10	10.2
H_a-19	2.35	3,6a	~1.9		
H_x-20	2.27	3,6e	~1.6		
H_y-20	1.49				
H_3-21	0.96				
OH	8.17				
OMe	3.72				

[a] higher order subspectrum

[b] unresolved long-range coupling interaction which is detected in the COSY-45 contour-plot, optimized for long-range couplings

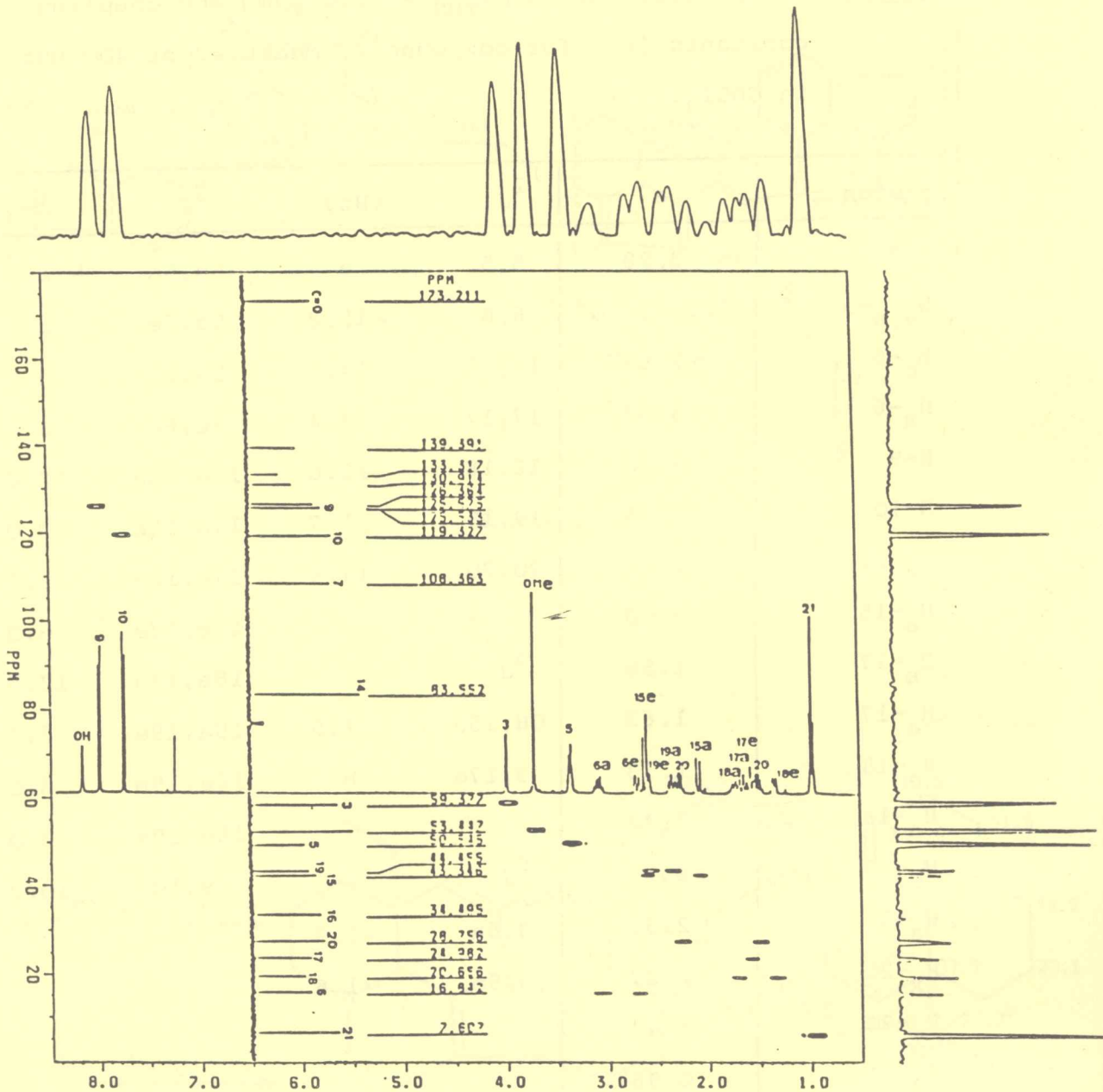


Figure 1. The ^{13}C-^{1}H hetero correlated contour plot for compound 2, measured at 9.4 Tesla. Insets show the normal ^{1}H spectrum (horizontal) and the broad-band ^{1}H decoupled ^{13}C spectrum (vertical).

Table II. Observed ^{13}C-^{1}H long-range correlation of quaternary carbons for compound 2.

	^{2}J	^{3}J
C-2	H-3	H_e-6
C-7	H_a-6, H_e-6	H-3
C-8		H-1O
C-11		H-9
C-12		H-1O
C-13		H-9
C-14	H_e-15, OH	
C-16	H_a-15, H_e-15, H-3	H_e-18
C=O		H_a-15, OMe, OH

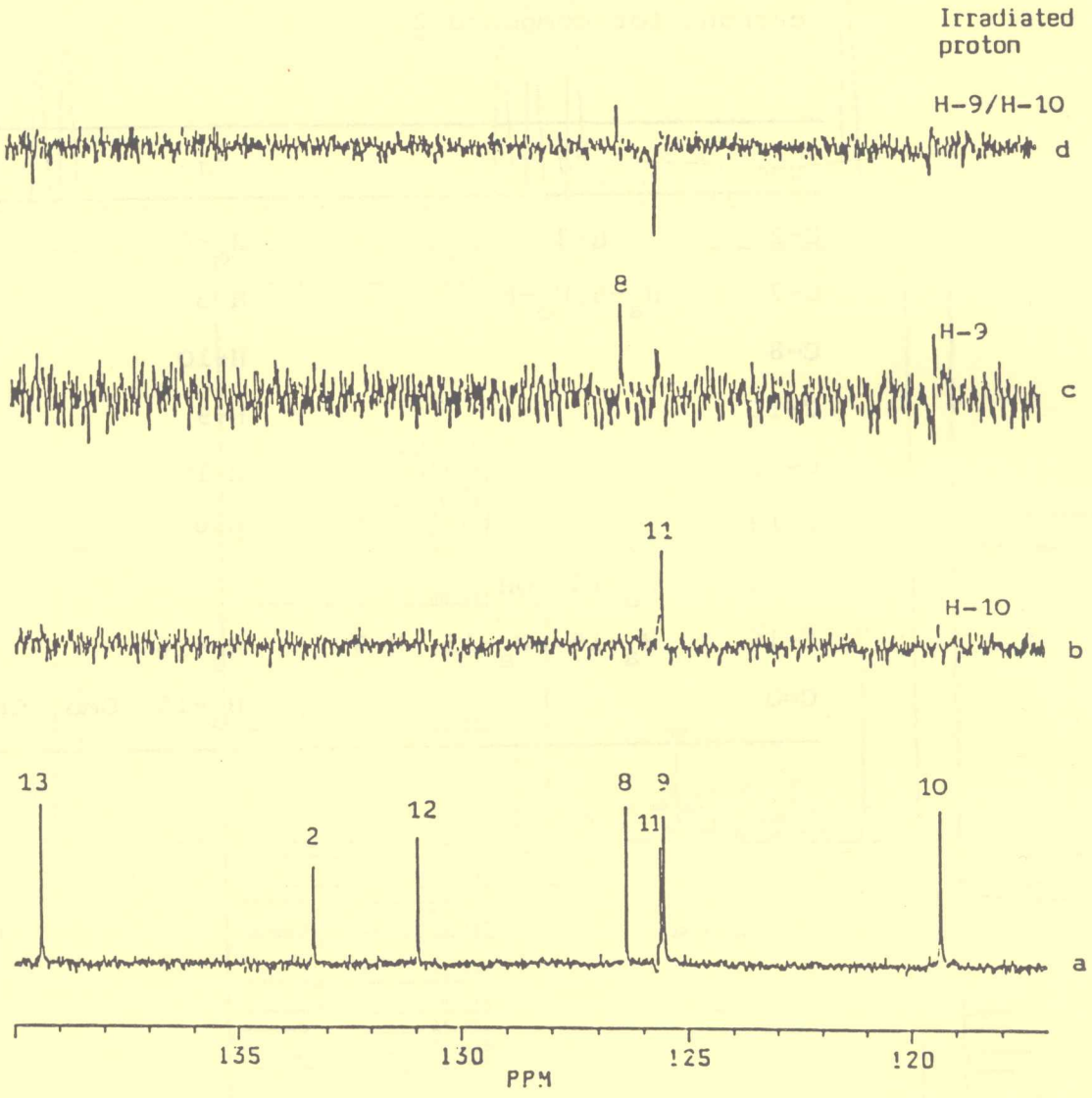


Figure 2. Heteronuclear NOE difference spectra for compound 2.

a./ Part of the low field region of the broad-band ^{1}H decoupled ^{13}C spectrum.

b./, c./ and d./: spectra gained when irradiating H-10, H-9 and H-10 or H-9 -see text.

Oxidation of 11-Aminovincamine into a Phenazine Derivative†

J. Chem. Research (S), 1990, 124–125†

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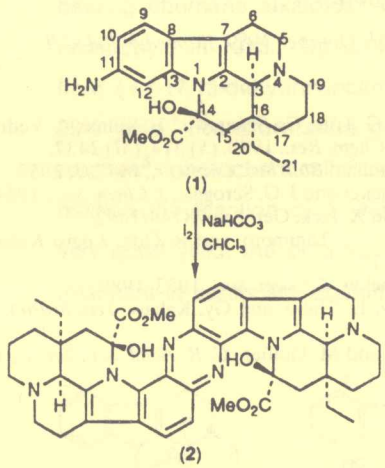
We find that the formation of phenazine derivatives from reaction of 11-aminovincamine with iodine does not involve an iodine substitution, the reaction proceeding *via* a dihydrophenazine derivative and involving two consecutive oxidation steps; support for the mechanism is provided by the use of different oxidation reagents.

We have earlier reported a unique formation of phenazine derivatives of some indole alkaloids; thus (+)-11-aminovincamine (**1**) was treated with iodine in a mixture of chloroform and saturated aqueous $NaHCO_3$ at room temperature and the phenazine derivative (**2**) was obtained (Scheme 1).[1] We suggested a reaction mechanism in which, as the first step, the 12-iodo compound is formed. This subsequently gives, by elimination of hydrogen iodide, the dihydrophenazine derivative (**3**), which is then oxidized to the end product (**2**).[1] Although the substitution of iodine, owing to steric reasons, seems to be much more favourable at the C-10 position than at C-12, we were not able to observe the appearance of either 11-amino-10-iodovincamine or a linearly condensed phenazine derivative, which, in principle also should be available from 11-amino-10-iodovincamine. Further investigations have now been carried out to determine the role of iodine in this reaction.



Scheme 1

It is known that dibenzo[*a*,*h*]phenazine (the angularly condensed product) is formed from β-naphthylamine[2] with oxidation reagents such as $Pb(CH_3CO_2)_4$,[3] $Ca(OCl)_2$,[4] O_2–KOBu^t,[5] and phenyl iodosoacetate.[6] The behaviour of (+)-11-aminovincamine against various oxidizing agents is also now reported. Selection of the reagents was based on the standard redox potential data, which should be near to that of the $2I^-/I_2$ system. In each case we obtained (**2**) resulting from oxidation. The reagents used and the parameters of the oxidation reactions are summarized in Table 1.

After treatment of (+)-9-aminovincamine with I_2 or Fetizon reagent (the most effective oxidation agent), we could detect no phenazine derivative in the reaction mixture. On the basis of our recent investigations we concluded that the reaction may take place through two consecutive oxidation steps. At first, (**4**), which has a quinoidal structure with a formal positive charge on the indole nitrogen (Scheme 2), is formed. Furthermore, C-12 is also positively polarized and will take part in a cyclodimerization of the HN=C(11)–C(12) moieties yielding the dihydrophenazine (**3**). The observed regioselectivity can be explained on the basis of the reduced reactivity of C-10. Additionally, nucleophilic attack of the imino group on C-10 would result in the linearly condensed product, which is unfavourable in accordance with the different stabilities of angularly and linearly condensed aromatic systems. This is also reflected in the reactions of β-naphthylamine[2–6] (mentioned above).

The appearance of the intermediate (**4**) accords with the observation that 11-aminovincamone does not give any phenazine under similar conditions. In this case, due to the presence of the N–C=O group, the indole nitrogen is positively polarized; this will make the formation of (**4**) rather hindered. From the proposed reaction mechanism it follows that, starting from optically active (**1**), an optically active product would be expected, which has C_2 symmetry (*i.e.* with the two ethyl and two ester groups on the same face of the skeleton). Although we could not detect any optical rotation, considerable Cotton effects were observed in the CD spectrum of (**2**). From the CD and UV spectral data of (**2**) (Table 2) it can be seen that at 546 and 578 nm, the wavelengths used for measuring the optical rotation, the measurement becomes insensitive because of the considerable UV absorption. When the measurement was repeated using a diluted solution on a more sensitive polarimeter, an optical rotation $[\alpha]_D^{25} = 329$ ($c = 1$, $CHCl_3$) was found.

We performed the oxidation with iodine starting from racemic (±)-11-aminovincamine. In this case the formation of two diastereoisomeric compounds can be expected, one with C_2 symmetry and the other with a C_1 inversion centre. However, we could not observe the presence of any second diastereoisomer by using TLC or ^1H or ^{13}C NMR methods. It is possible that in these two isomers the chemical shift differences are too small to detect owing to the remote centres of chirality. Using $Eu(fod)_3$ shift reagent some minor signals (*ca.* 15% intensity) appeared in the ^{13}C NMR spectrum.

Experimental

For preparative chromatography a Merck Kieselgel 60 column was used. Optical rotations were measured in chloroform at 25 ± 2 °C on Polamat A and Perkin-Elmer model 241 polarimeters. CD spectra were recorded on a Jobin-Yvon Mark III Dichrograph in acetonitrile ($c = 0.301$ mol ml^{-1}, 5 mm pathlength). NMR spectra were recorded on a Bruker AC-250 spectrometer in $CDCl_3$.

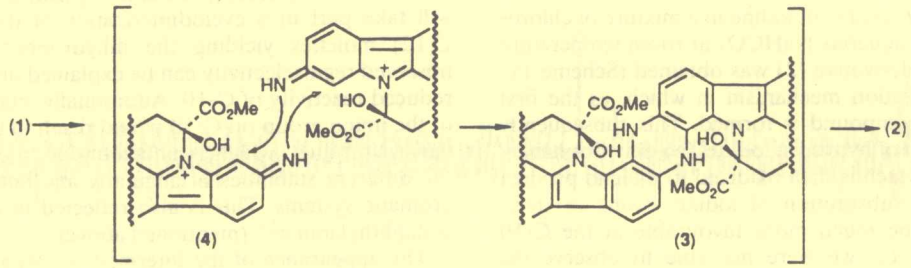
Dimethyl (11*S*,12a*S*,18c*R*,23*S*,24a*S*,24b*R*)-(12a,24a-*diethyl*-11,23-*dihydroxy*-1,2,3,5,6,11,12,12a,13,14,15,17,18,18c,23,24,24a,24b-*octadecahydrobis*{*quinolizino*[2′,1′,9a′,9:1,8a,8,7]*indolizino*}[3,2-a][3,2-h]*phenazine*-11,23-*dicarboxylate*) (**2**). *General Procedure.*—The starting material was dissolved in an organic solvent or in a two-phase aqueous system and treated with the oxidising agent. In the case of the two-phase aqueous system the use of a catalyst

*To receive any correspondence.
†This is a Short Paper as defined in the Instructions for Authors [*J. Chem. Research (S)*, 1990, Issue 1, p. ii]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 1 Reagents used and the parameters of the oxidation reactions

Starting material	Oxidation reagent	Solvent	Temperature (°C)	Reaction time (h)	Catalyst	Method	Yield (%)
(+)-(**1**)[a]	$PbAc_4$	CH_3CO_2H	25	1	—	B	2.6
	Bu^tOCl	CCl_4–H_2O/$NaHCO_3$	25	1	—	B	3.2
	$FeCl_3$	$CHCl_3$–H_2O	25	2	Bu^tNH_4Br	A	11
	$KMnO_4$	$CHCl_3$–H_2O	25	2	Bu^tNH_4Br	A	33
	$AgNO_3$	$CHCl_3$–H_2O	25	2	Bu^tNH_4Br	A	18
	MnO_2/Celite	xylene	140	1	—	B	25
	Fetizon reagent[b]	xylene	140	1	—	A	35
	I_2	$CHCl_3$–H_2O/$NaHCO_3$	25	2	—	A	30[c]
(±)-(**1**)[a]	I_2	$CHCl_3$–H_2O/$NaHCO_3$	25	2	—	A	29

[a]Ref. 7. [b]Ref. 8. [c]Ref. 1.



Scheme 2

Table 2 CD and UV spectral characteristics of (**2**)

λ/nm	Δε	λ/nm	ε
203.2	10.084	271.1	37 000
236.4	0.913	322.5	65 000
265.9	−11.029	333.3	21 000
319.5	2.795	443.2	13 000
345.4	0.112	513.3	11 000
398.4	−0.124		
511.7	−2.440		
567.3	−0.203		

was advantageous. When the reaction was complete, the reaction mixture was washed with ammonia solution and water. After drying, the pure material was isolated by crystallization (A) or by column chromatography (B) on silica (eluant $CHCl_3$–MeOH, 19:1 v/v).

We thank Dr. M. Kajtár for the CD spectrum and to the OTKA program of the Hungarian Academy of Sciences for financial support.

Received, 17th October 1989; Paper E/9/04477I

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SYNTHETIC COMMUNICATIONS, 21(8&9), 965-967 (1991)

SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. PART LVIII[1]. A NOVEL FORMAL SYNTHESIS OF (-)-CRIOCERINE FROM (+)-VINCAMINE

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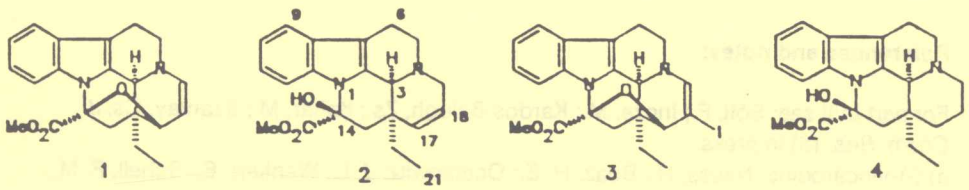
Abstract: 18-Iodo criocerine (3), a synthetic precursor to (-)-criocerine (1), was prepared from (+)-vincamine (4) via a new one-step procedure. Full ^{1}H and ^{13}C NMR assignments for 3 are also given.

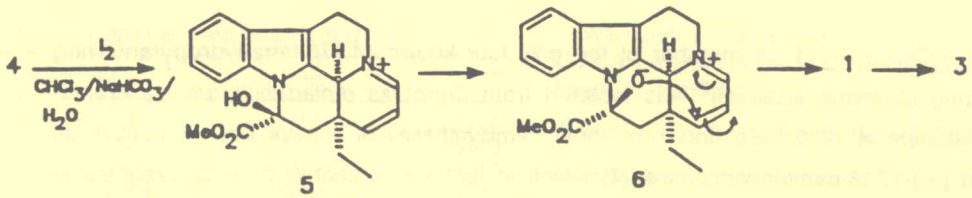
(-)-Criocerine (1), a member of the only four known 14,17β-tetrahydropyranyl ring bearing eburnane alkaloids[2] was isolated from *Crioceras dipladeniiflorus* by French researchers in 1975.[3] Up until now three hemisyntheses of 1 have been reported, all from (+)-17,18-dehydrovincamine (2) which in turn was prepared from tabersonine in 29% yield.[4] Transformation of 2 into 1 was carried out by the modified Polonovski reaction[3], photochemically[5], or via 18-iodo criocerine (3)[4]. According to the third method the reaction of 2 with iodine in the presence of potassium iodate gave 3 in very good yield; the obtained iodo derivative 3 was then transformed into 1 by acidic treatment in essentially quantitative yield.



Whilst exploring the application of iodine[6] in the transformation of Vinca alkaloid derivatives, we have found that the iodo criocerine precursor **3** can easily be obtained directly from **4** (the latter is being produced on an industrial scale) with the iodine performing a double oxidation. The presence of a double bond in ring D is therefore not a prerequisite to the given transformation. It is noted, however, that vincamine (**4**) could be transformed into **1** photochemically, but in rather poor yield (12%)[5].

Upon treatment of **4** (1.4 g : 4 mmol) with iodine (4.3 g : 17 mmol) in a mixture of chloroform and saturated aqueous $NaHCO_3$ (60/30 ml) for 2 hrs at room temperature, work-up of the reaction mixture (treatment with 10% $Na_2S_2O_3$ solution, washing with water, evaporation, crystallization from ether) gave **3**[7] in 77% yield. Compound **3** can easily be transformed into **1**.[4]

With regard to the reaction sequence we can safely assume the formation of tetrahydro-vincamine (**5**) as an intermediate. After deprotonation the oxygen attacks the γ carbon following the well established route of halohydrine formation. However, we do not rule out that an intramolecular reaction might result first in the formation of **1** followed by iodination affording the end-product **3**, since direct iodination of **1** leading to **3** is a known transformation.[4]



The extension of this new method to other alkaloids and the investigation of the role of the starting materials are in progress.

Acknowledgment: The authors wish to thank J. Tamás for the mass spectrum and Ms K. Welker for technical assistance.

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7. The physical constants of **3** were identical with those reported in ref. 4. However, since those authors gave only two ^{1}H signals for the NMR characterization of **3**, here we list the full ^{1}H and ^{13}C assignments of this compound, as determined by a combination of high-field [300 MHz (^{1}H)] NMR methods (COSY, HETCOR, DNOE):
^{1}H NMR ($CDCl_3$), δ (ppm): 1.03 (3H, t, H_3-21); 1.53 (1H, dq, H_x-20); 1.75 (1H, dq, H_y-20); 2.43 (1H, d, Hβ-15); 2.68 (1H, m, Hα-6); 2.77 (1H, m, Hβ-6); 2.83 (1H, d, Hα-15); 3.36 (1H, ddd, Hα-5); 3.65 (1H, dd, Hβ-5); 4.05 (3H, s, OMe); 4.30 (1H, d, H-17); 4.39 (1H, brs, H-3); 6.31 (1H, s, H-19); 6.97 (1H, m, H-12); 7.08-7.15 (2H, m, H-10, H-11); 7.38 (1H, m, H-9).

   ^{13}C NMR ($CDCl_3$), δ(ppm): 9.1 (C-21); 21.4 (C-6); 24.9 (C-20); 45.6 (C-16); 45.7 (C-15); 49.8 (C-5); 53.3 (OMe); 53.3 (C-3); 63.0 (C-18); 85.2 (C-17); 90.9 (C-14); 111.5 (C-7); 111.8 (C-12); 118.4 (C-9); 121.1 (C-10); 122.7 (C-11); 130.9 (C-8); 134.9[a] (C-13); 137.5[a] (C-2); 168.6 (CO). [[a] = tentative assignments]

   A notable feature of **3** is that δ(C-6) is shifted downfield of its δ *ca.* 16 ppm value typical of the *cis* D/E ring-fused eburnane skeleton[8]. This downfield shift is due to the loss of the γ-gauche interaction between C-19 and C-6 as a result of the enamine character of N-4[9].

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(Received in UK 11 February, 1991)

SYNTHETIC COMMUNICATIONS, 22(4), 509-512 (1992)

SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. PART LIX[1]. A NOVEL HEMISYNTHESIS OF (-)-CRASPIDOSPERMINE

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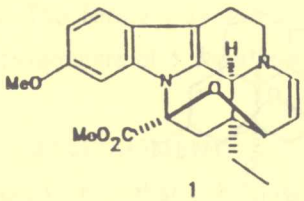
Abstract: (+)-Vincine (3) has been transformed into (-)-craspidospermine (1) via (-)-18-iodo craspidospermine (4).

(-)-Craspidospermine (1), one of the known alkaloids of the plant *Craspidospermum verticillatum* (Madagaskar) was isolated by French researchers in 1976[2] and the hypothetic structure was verified by hemisyntheses[2,3,4]. Compound 1 was prepared from (+)-17,18-dehydrovincine (2)[5], an alkaloid isolated from the same plant, by the modified Polonovski reaction[2,3] and photochemically[4].



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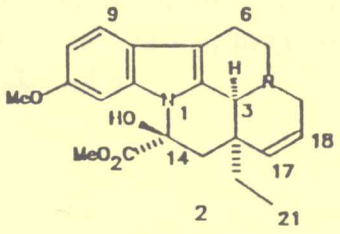
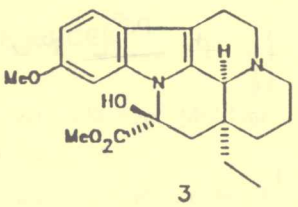


2



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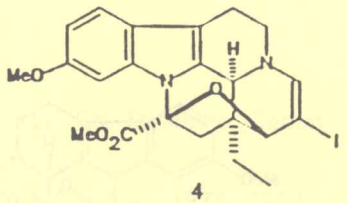
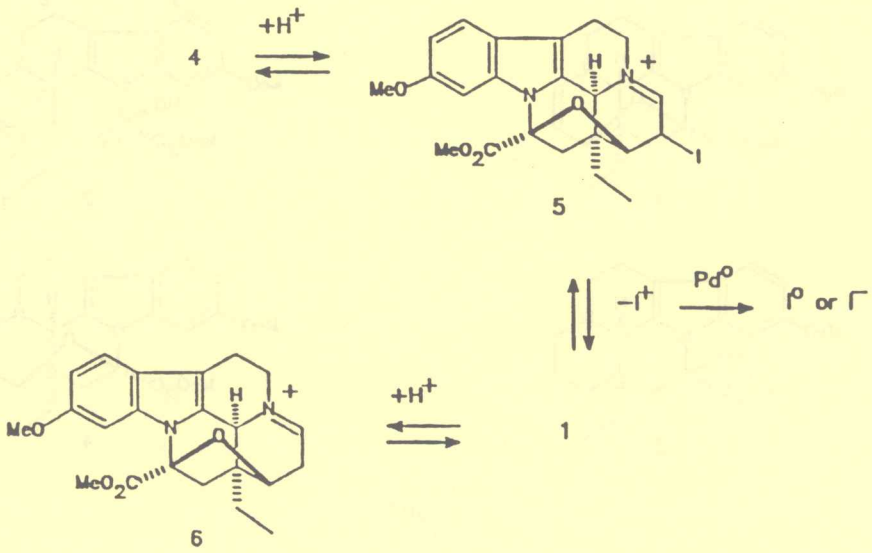


4

In our previous communication[6] we described a simple method for constructing the 14,17β-tetrahydropyranyl ring with the aid of iodine and starting from vincamine (i.e. the 11-demethoxy analogue of **3**). In this regard we have pointed out that the presence of the C-17=C-18 double bond in the starting material is not a prerequisite to the complex reaction involving a double oxidation in ring D, formation of an oxygene bridge between C-17 and C-14, formation of the enamine function in ring D, and subsequent iodination of the enamine. By extending the application of this new method to other alkaloids we have found that (+)vincine **3**[7] can easily be transformed into (-)-18-iodo craspidospermine (**4**) in 92 % yield. Compound **4** can therefore be obtained directly from **3** instead of **2**; this may be of interest considering that **3** is a much more accessible alkaloid than **2**.

The iodo derivative **4** proved to be a good synthetic precursor to **1**. For the deiodination of the β-iodo enamine function in **4** a reductive method (Pd/C in formic acid) was applied instead of an acidic reflux that was proposed in the literature[8] for this type of compounds. In this case **4** affords **1** in nearly quantitative yield (91%). A possible mechanism for the reduction of **4** is the following. The starting β-iodo enamine exists in an enamine **4** ⇌ iminium **5** equilibrium in the protic solvent (formic acid). The iminium form **5** facilitates the elimination of iodonium cation which is then reduced by metal (palladium). In principle the stable enamine has a further, deiodinated iminium form **6**. After basic treatment of the reaction mixture the more stable enamine **1** can be isolated.



Further results in this field will be published elsewhere.

EXPERIMENTAL

(-)-18-iodo craspidospermine (4): (+)-Vincine (3, 85 mg; 0.22 mM) was dissolved in a mixture of chloroform and saturated aqueous $NaHCO_3$ (4 ml / 2 ml) and iodine (0.23 g; 0.9 mM) was added and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was treated with 10% $Na_2S_2O_3$ solution, washed with water and dried (Na_2SO_4). The filtrate was evaporated to dryness to give **4** (103 mg; 92 %) as a pure oil.

$[\alpha]_D = -39.7$ (c = 0.1; $CHCl_3$). IR (KBr) : 1740 (carbonyl), 1605 (enamine).

UV (EtOH) : 228 (4.23); 262 (3.78); 296 (3.42).

MS : 506 (69.8, M^+); 380 (30.0); 379 (100.0, M-27); 200 (16.3, M-306); 142 (31.3).

^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.03 (3H, t, H_3-21); 1.52 (1H, dq, H_x-20); 1.76 (1H, dq, H_y-20); 2.41 (1H, d, Hβ-15); 2.67 (1H, m, Hα-6); 2.75 (1H, m, Hβ-6); 2.80 (1H, d, Hα-15); 3.38 (1H, ddd, Hα-5); 3.64 (1H, dd, Hβ-5); 3.77 (3H, s, 11-OMe); 4.05 (3H, s, COOMe); 4.30 (1H, d, H-17); 4.39 (1H, brs, H-3); 6.31 (1H, s, H-19); 6.50 (1H, d, H-12); 6.75 (1H, dd, H-10), H-11); 7.24 (1H, d, H-9).

(-)-Craspidospermine (1): Compound **4** (70 mg; 0.138 mM) was dissolved in formic acid (2 ml) and palladium on carbon (70 mg) was added and the reaction mixture was stirred for 24 h at room temperature under N_2. After filtration the filtrate was poured into aqueous ammonium hydroxyde solution and was extracted with CH_2Cl_2 (3 x 5 ml). The combined organic phase was washed with water and dried (Na_2SO_4). The filtrate was evaporated to dryness to give **1** (oil; 48 mg; 91%). The physical parameters of **1** were identical with those reported in ref. 2.

ACKNOWLEDGEMENT

The authors wish to thank J. Tamás for the mass spectra.

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(Received in UK 5 August, 1991)

A POLONOVSKI-REAKCIÓ ALKALMAZÁSA EBURNÁNVÁZAS VEGYÜLETEK KÖRÉBEN

Tetrahedron Letters,Vol.27,No.24,pp 2775-2778,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XXXI[1]
UNUSUAL POLONOVSKI REACTION OF SOME VINCA ALKALOIDS

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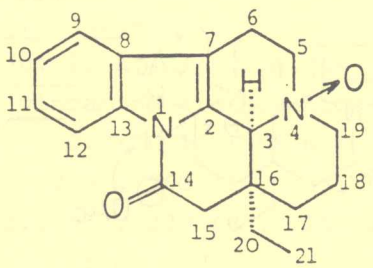
Abstract: *In the course of the Polonovski reaction of some indole alkaloids a new type of dimerization has been found.*

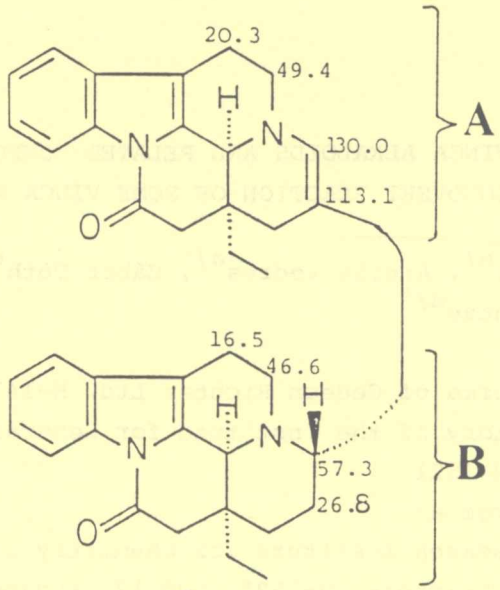
The Polonovski reaction and its modification by P. Potier are widely used in alkaloid chemistry[2]. Starting from systems containing ß-carboline moiety the reaction usually leads to the corresponding imminium salts. E.g. on converting eburnamonine into its N-oxide and on treatment of the latter with trifluoroacetic anhydride the corresponding imminium salt was obtained, which on reduction gave rise to trans-eburnamonine[3].

In view of these results we were surprised to find an entirely different behaviour of vincamone N-oxide[3] (1). When 1 (40 mmol) was treated with acetic anhydride (0.53 mol; 50 ml) at room temperature for 24 h crystals of the dimeric indole derivative 2[4] precipitated in 52 % yield.



1

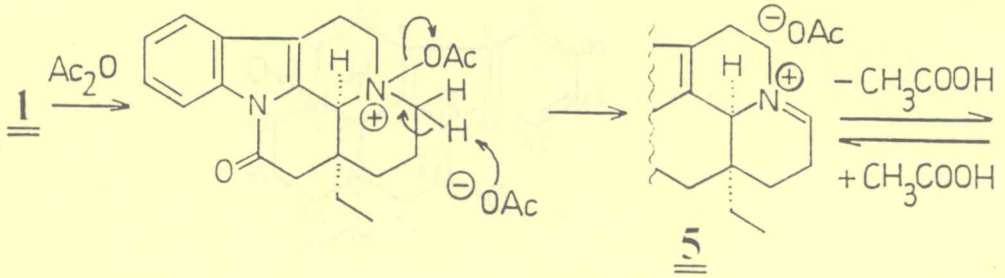
Some of the ^{13}C-NMR shifts are indicated at the corresponding carbon atoms.



2

Results were similar when the N-oxides of the alkaloid vincamine[5] and of apovincaminic acid ethyl ester[5] were reacted with acetic anhydride. The obtained dimers (3[6] from vincamine N-oxide[7] and 4[8] from apovincaminic acid ethyl ester N-oxide[9]) have structures similar to 2, thus the reaction seems to be rather general.

A possible reaction sequence leading to the dimers may be the following. The electrophilic imminium salt 5 and the nucleophilic enamine 6 both present in equilibrium in solution react with each other yielding the end product after deprotonation.



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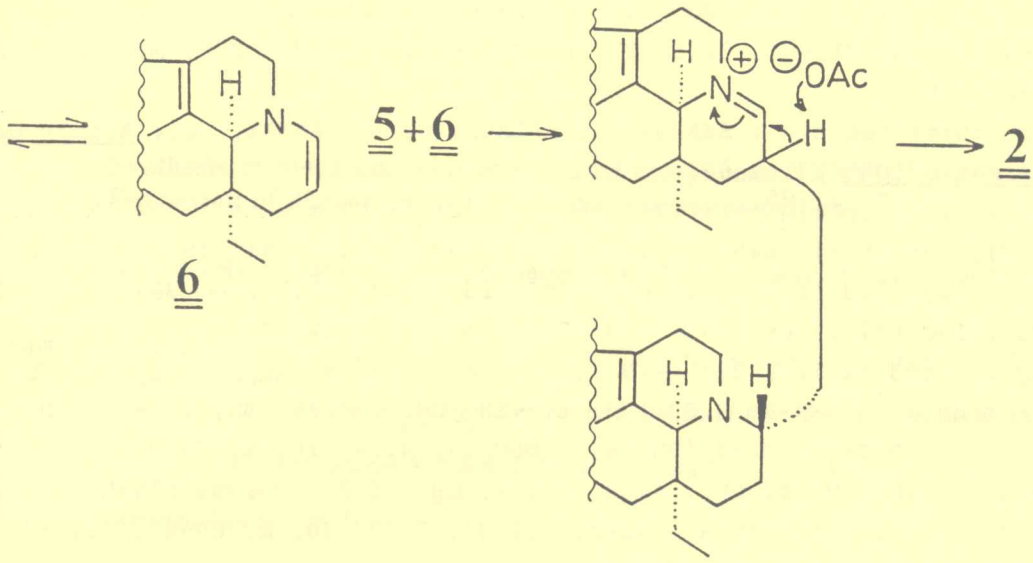

In order to substantiate the supposed mechanism the separately prepared enamine 6[10] was treated with acetic acid. The reaction indeed provided dimer 2, as expected.

Using the modified conditions of the Polonovski reaction (i.e. trifluoroacetic anhydride in CH_2Cl_2) 1 gave 2 only in a very low yield in addition to other products.

Investigations concerning the scope and limitation of the above reaction sequence are in progress.

A detailed discussion of the NMR data will be published later.

Acknowledgement: The authors wish to thank J. Tamás and M. Mák for mass spectra.

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   Note that eburnamonine and vincamone are enantiomers.
4. mp 304-306 °C; $[\alpha]_D^{25}$=-345.4° (c=0.2;$CHCl_3$); MS m/e (%): 584 (M^+, 53), 556 (6), 555 (7), 527 (1.3), 526 (2.5), 360 (1), 331 (100), 330 (18), 318 (5), 301 (10), 292 (34; M/2), 263.5 (5), 238 (6), 224 (28), 196 (3), 181 (4), 180 (4), 168 (8), 167 (8); UV (EtOH + HCl): λ_{max} [nm], (lgε): 202 (4.69), 240 (4.60), 265 (4.24), 300 (3.97); IR (KBr): 1700, 1610, 1670 [cm^{-1}];

^{1}H-NMR (The NMR spectra have been recorded on a Jeol FX-100 instrument in $CDCl_3$) δ: 0.87 (3H, t, $-CH_2-C\underline{H}_3$), 0.98 (3H, t, $-CH_2-C\underline{H}_3$), 3.80 (1H, s, C3-H), 4.10 (1H, s, C3-H), 5.80 (1H, s, C19-H ; in part A), 7.10-7.50 (6H, m, C9-H, C10-H, C11-H), 8.35 (2H, m, C12-H) 1.10-3.70 (23H, m, skeletal + + $-C\underline{H}_2-CH_3$).

5. Structures see e.g.: SZABÓ, L.; KALAUS, Gy.; SZÁNTAY, Cs.: Archiv der Pharmazie 1983 (316) 629

6. mp 246-249 °C; $[\alpha]_D^{25}$=-141,1° (c=0.2; $CHCl_3$); MS m/e (%): 704 (M^+,88), 686 (3.3), 675 (5.6), 645 (14), 644 (23), 585 (9.3), 584 (18), 391 (100), 352 (50; M/2), 343 (18), 331 (65), 292 (16), 284 (21), 266 (36), 224 (40), 208 (25), 170 (17), 169 (14), 168 (20), 167 (17); UV (EtOH + HCl): λ_{max} [nm], (lg ε): 203 (4.52), 224 (4.82), 276 (4.19) ; IR (KBr): [cm^{-1}] 1720, 1650 (enamine); ^{1}H-NMR δ: 0.83 (3H, t, $-CH_2-C\underline{H}_3$), 0.96 (3H, t, $-CH_2-C\underline{H}_3$), 3.75 (3H, s, $-COOC\underline{H}_3$), 3.84 (3H, s, $-COOC\underline{H}_3$), 4.04 (1H, s, C3-H), 4.80 (1H, s, C3-H), 3.40 (1H, s, O$\underline{H}$), 4.54 (1H, s, O$\underline{H}$), 5.80 (1H, s, C19-H; in part A), 7.00-7.75 (6H, m, C10-H, C11-H, C12-H), 7.47 (2H, m, C9-H), 1.10-3.70 (23H, m, skeletal + $C\underline{H}_2-CH_3$).

7. Fr. Demande 2.162.282 (Synthelabo S. A.) / C. A. 1974 (80) 19 575 g

8. mp 220-221 °C ; $[\alpha]_D^{25}$=-209.6° (c=0.2; $CHCl_3$); MS m/e (%): 696.365 (M^+, 43), 667 (5), 651 (2), 638 (1), 623 (2), 594 (0.5), 526 (0.5), 429 (1.4), 416 (3), 387.2080 (81), 374 (8), 357 (6), 348 (26; M/2), 308 (3), 294 (6), 281 (24), 280 (100), 252 (24); UV (EtOH + HCl): λ_{max} [nm], (lgε): 204 (4.66), 226 (4.73), 271 (4.31), 316 (4.04) ; IR (KBr): 1730, 1680, 1640 [cm^{-1}]; ^{1}H-NMR δ : 0.95 (3H, t, $-CH_2-C\underline{H}_3$), 1.08 (3H, t, $-CH_2-C\underline{H}_3$), 1.35 (3H, t, $-COOCH_2C\underline{H}_3$), 1.40 (3H, t, $-COOCH_2C\underline{H}_3$), 4.40 (2H, q, $-COOC\underline{H}_2CH_3$), 4.38 (2H, q, $-COOC\underline{H}_2CH_3$), 3.94 (1H, s, C3-H), 4.30 (1H, s, C3-H), 5.82 (1H, d, J=1.7 Hz, C19-H; in part A), 6.10 (1H, s, C15-H), 6.36 (1H, s, C15-H), 7.00-7.30 (6H, m, C10-H, C11-H, C12-H), 7.45 (2H, m, C9-H), 1.20-3.80 (19H, m, skeletal + $C\underline{H}_2-CH_3$).

9. SZABÓ, L.; SZÁNTAY, Cs.; et al.: unpublished results

10. BENCELMANS, R.; HERLEM, D.; HUSSON, H.-P.; KHUONG-HUU, F; LE GOFF, M.-T.: Tetrahedron Letters 1976 435

(Received in UK 10 April 1986)

Recueil des Travaux Chimiques des Pays-Bas, 107/4, April 1988 335

Recl. Trav. Chim. Pays-Bas **107**, 335–342 (1988) 0165–0513/88/04335–08$2.50

Synthesis of vinca alkaloids and related compounds XXXVIII[1]. Formation of dimers under Polonovski reaction conditions

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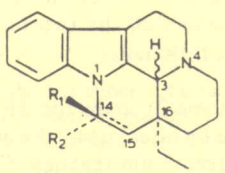
(Received October 5th, 1987)

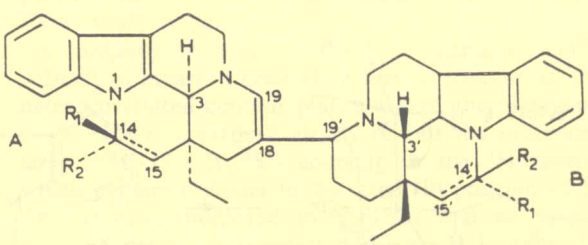
Abstract. The dimeric products (**1a-c**) have been prepared by treatment of *N*-oxides derived from some indole alkaloids. Their structures have been elucidated by detailed NMR investigations and the structure of **1c** determined by X-ray analysis. The importance of the E_2-type *trans*-axial elimination of the *N*-acyloxy intermediate in the dimer formation has also been established. The iminium salts **4a-b** and the derived pseudocyanide **6** have been prepared.

In a preliminary communication[2] we have described the formation of dimeric products **1a-c** by treatment of *N*-oxides derived from vincamone (**2a**), vincamine (**2b**) and apovincaminic acid ethyl ester (**2c**) with acetic anhydride.
On water elimination and transesterification, **1b** can be transformed into **1c**.
It was shown that the most likely pathway for this dimer formation involves the interaction of intermediate enamine (*e.g.* **3**) with the corresponding iminium salt (*e.g.* **5**). Similar dimerizations with related molecules under different conditions have been previously observed[3].
In order to support the presumed reaction mechanism, enamine **3** was prepared as described in the literature[4] using a photochemical method, but in poor yield. It was found, however, that treatment of vincamone *N*-oxide (**2f**) with $K_2Cr_2O_7$[5] afforded the desired enamine in 45% yield[6]. In the first step, probably an E_2-type elimination occurs from the chromic ester and thus stereoelectronic factors favour the formation of kinetic iminium ion **5** instead of the thermodynamically more stable **4a**. The basification of **5** yields **3**, which gives rise to **1a** with acetic acid.
Iminium salt **5** was characterized through the formation of pseudocyanide **6** in 33.5% yield. The nitrile group in **6** is axial, which indicates a kinetically controlled attack of the nucleophile on the carbon–nitrogen double bond.
Treatment of the *N*-oxide **2h** with $K_2Cr_2O_7$ did not give the easily separable crystalline enamine as did the same treatment of **2f**, and subsequent chromatography afforded dimer **1c**, formed presumably in the course of chromatography[6].
To investigate the scope and limitations of the dimer formation under *Polonovski*-type reaction conditions, the modi-



2a-j

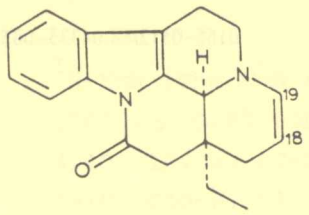
Compound	R-1(+ R-2)	H-3	C-14⊖C-15	N-4-oxide
a	O	α	single bond	f
b	OH + $COOCH_3$	α	single bond	g
c	$COOC_2H_5$	α	double bond	h
d	O	β	single bond	i
e	$COOCH_3$	β	double bond	j



1a-c

Compound	R^1 (+ R^2)	C-14 ⊖ C-15
a	O	single bond
b	OH + $COOCH_3$	single bond
c	$COOC_2H_5$	double bond
d	$COOCH_3$	double bond

Scheme 1. Structure of dimeric products **1a-c**.



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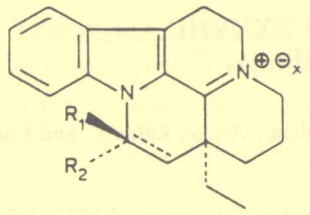


4a-b

Compound	R-1 (+ R-2)	C-14⊖C-15
a	O	single band
b	$COOCH_3$	double band

fied version[7], using trifluoracetic anhydride, was first investigated. In contrast to the statement of a Belgian patent[8], no iminium salts (**4**) were found, and only the dimers **1** were isolated in rather poor yield.

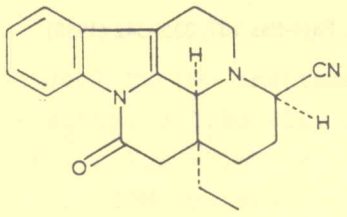
A dramatic change was observed, however, when the reaction was carried out with the *trans* series instead of the natural *cis* compounds.

When the *N*-oxide of *trans*-vincamone (**2i**) or *trans*-apovincamine (**2j**) was treated with trifluoroacetic anhydride, iminium salts **4a** and **4b** were obtained, respectively, as main products. Not a trace of dimer could be isolated.

The difference in the behaviour of the two (*cis* and *trans*) types of compounds can be rationalized by consideration of stereoelectronic factors.

In the *cis*-series (see Scheme 2), only the H_{ax}-19 of the *N*-acyloxy intermediate can be attacked by the acylate anion in an E_2-type *trans*-axial elimination reaction. On the other hand, in the *trans* series (Scheme 3), in addition to the above bond, the H_{ax}-5 and H-3 bonds are also in the appropriate stereoposition and, since the elimination of the latter leads to the thermodynamically most stable iminium salt, presumably the transition state energy requirement is the lowest for this particular reaction.

Our findings support the importance of E_2-type stereoelectronic requirements in the key-step of the Polonovski reaction.



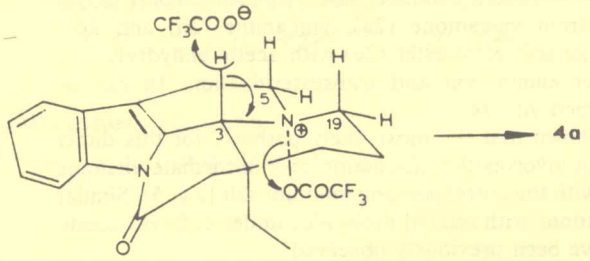
6

Structure determinations

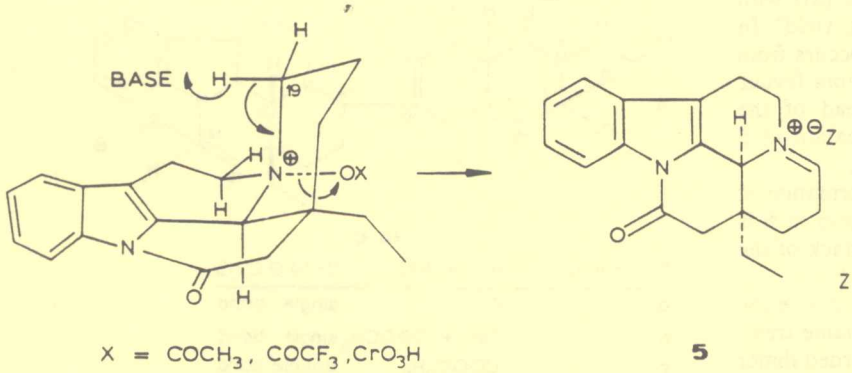
1. *NMR spectroscopy*

The structures of the dimeric compounds were first deduced from detailed ^1H and ^{13}C NMR studies of compound **1a**. The presence of the characteristic H-3 singlets (δ 4.13 and 3.82), the sharp vinylic proton signal at δ 5.82 and the three CH carbon signals between δ 55–59 ppm etc. all pointed to the suggested dimeric structure (Scheme 1). (This type of structure was later confirmed by X-ray analysis of compound **1c**; *vide infra*.)

In order to eliminate some of the uncertainties in the ^1H assignments (400 MHz) owing to the presence of the two similar units in the molecule, two-dimensional proton–proton correlation maps were also recorded: a COXY-45[9] spectrum at 360 MHz and one at 250 MHz, the latter optimized in order to reveal the presence of weak long-range coupling interactions. These correlations gave excellent starting points for tracing the homonuclear scalar connectivities in the various sub-spin systems. For example, the vinylic proton H-19 in unit A (δ 5.82) shows allylic couplings to the $H_{a,e}$-17 protons (δ 1.85 and 1.67), a "W" coupling with H-3 (δ 4.13) (the other characteristic H-3'* singlet (δ 3.82) is thus also assigned) and a further allylic coupling to H-19' of unit B, buried among other overlapping multiplets (δ 2.60–2.76). The respective coupling correlations of the above-mentioned signals (see Table II) readily led to the assignments given in Table I.



Scheme 3. Formation of the thermodynamically most stable iminium salt **4a**.



X = $COCH_3$, $COCF_3$, CrO_3H

5

Scheme 2. Kinetically controlled formation of iminium salt **5**.

* Accent (') indicates unit B.

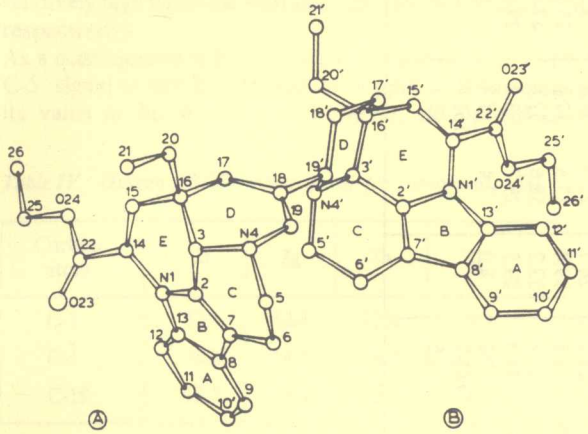


Fig. 1. A perspective view of dimer **1c** *showing the atomic labelling. The numbers are for carbon atoms, unless indicated otherwise. The H atoms are deliberately omitted. (The configuration presented is chosen in accordance with that of the natural vincamine skeleton.)*

Most of the ^{13}C assignments for **1a** were clarified by 2D C,H correlation measurements[10] (62.5/250 MHz) which also allowed the secure assignments of some very closely spaced signals (*e.g.* C-17, C-17′ and C-18′); see Table III. Monomeric indole derivatives **2a** and **3** were used as reference compounds. Assignments of the ^1H NMR spectra (400 MHz) were straightforward (see Tables I and II). (The ^1H chemical shifts for **2a** are consistent with those reported elsewhere[11].) ^{13}C signals were assigned (Table III) by using

Table I ^1H *chemical shifts for compounds* **1a**, **2a** *and* **3** *(400 MHz, $CDCl_3$, δ_{TMS} 0.00 ppm).*

Proton	**1a**		**3**	**2a**[a]
	unit A	unit B		
H_a-3	4.13	3.82	4.14	3.97
H_e-5	3.57	2.36–2.58	3.59	3.32
H_a-5	3.30	2.36–2.58	3.32	3.23
H_e-6	2.60–2.76	2.13	2.58	2.47
H_a-6	2.60–2.76	2.36–2.58	2.73	2.90
H-9	7.42	7.42	7.39	7.31
H-10	7.25–7.35	7.25–7.35	7.27	7.26
H-11	7.25–7.35	7.25–7.35	7.30	7.30
H-12	8.35	8.35	8.35	8.36
H_e-15	2.84	2.55	2.77	2.67
H_a-15	2.69	2.55	2.62	2.57
H_e-17	1.85	1.48	1.58–1.78	1.48
H_a-17	1.67	1.10 1.18 (eq.)	1.58–1.78	1.04 1.38 (eq.)
H-18	–	~1.63 (ax.) –	4.45	1.76 (ax.) 2.58 (eq.)
H-19	5.82	2.60–2.76 (ax.)	5.84	2.41 (ax.)
H_x-20	1.60	2.02	1.58–1.78	2.04
H_y-20	1.60	1.48	1.58–1.78	1.66
H_3-21	0.99	0.87	0.98	0.93

[a] See also ref. 12.

Table II Selected coupling constants (Hz) for compounds **1a**, **2a** *and* **3** *(400 MHz).*

^xJ(H-*y*–H-*z*)	**1a**		**3**	**2a**
	unit A	unit B		
^2J 5–5	13.9	[b]	14.0	13.9
6–6	[b]	15.8	16.1	16.9
15–15	17.0	[b]	17.0	16.6
17–17	[b]	14.0	17.0	13.4
18–18	–	[b]	–	13.4
19–19	–	[b]	–	10.7
20–20	[b]	14.3	[b]	14.4
^3J 5a–6a	10.7	[b]	11.5	10.6
5a–6e	5.5	[b]	4.7	5.7
5e–6a	5.0	[b]	6.0	6.6
5e–6e	<1	[b]	<1	<1
18–17e (α)	–	–	5.6	–
18–17a (β)	–	–	2.8	–
18–19	–	–	7.8	–
17a–18a	–	~14.0	–	13.4
17a–18e	–	[b]	–	3.9
17e–18a	–	[b]	–	3.4
17e–18e	–	[b]	–	3.1
18a–19a	–	[b]	–	12.5
18a–19e	–	–	–	3.2
18e–19a	–	[b]	–	2.9
18e–19e	–	–	–	3.2
^4J 3–17e	[a]	[a]	~2.4	1.6
19–17a	~2.0	–	2.4	–
19–17e	[a]	–	[b]	–
3–19	[a]	–	[b]	–
3–19e	–	–	–	~1
17e–19e	–	–	–	1.6
19–19′a	[a]	–	–	–
^5J 3–6a	[a]	[a]	3.2	2.9
3–6e	[a]	[a]	2.2	2.6

[a] Small coupling which is either not clearly resolved, or concealed by overlapping. The corresponding long-range correlations are detected in the COSY spectra. [b] Unreliably measured, mainly because of overlapping.

2D C,H correlation maps (measured at 25/100 MHz for **3** and at 100/400 MHz for **2a**).

A comparison of the ^1H and ^{13}C NMR shifts of **1a** with those of **2a** and **3** supports the deduced dimeric structure. Note, that the $H_{a,e}$-5′ signals (unit B) are shifted *ca.* 0.8 ppm upfield from their values in **2a**. This might be attributed to the shielding effect of the indolic part of unit A, which passes "above" these protons during rotation around the C-18–C-19′ bond.

The coupling constants of the H-19′ signal in unit B are difficult to measure because of serious overlap. In the 2D heterocorrelated contour plot, however, the corresponding C-19′–H-19′ crosspeak clearly reveals the presence of a large $J(H_a\text{-}19'\text{–}H_a\text{-}18')$ coupling in the ^1H dimension, which evidently points to the axial (β) position of H-19′. This is also supported by the fact that no long-range coupling interaction is detected between H-3′ and H-19′ (*cf.* $^4J(H\text{-}3\text{–}H_e\text{-}19) \sim 1$ Hz, arising from the "W" pathway in **2a** – Table II).

Note that in unit A, as well as in **3**, δ(C-6) is shifted downfield relative to its δ *ca.* 16 ppm value, characteristic of the eburnane skeleton possessing *cis* D/E (and consequently *cis* C/D) ring fusions[12]. This downfield shift can be explained by the loss of the γ-gauche interaction between C-19 and C-6, owing to the "enamine" character of N-4. Nevertheless, the *cis* D/E ring fusion of unit A and **3** is reflected by the

Table III ^{13}C *chemical shifts for compounds* **1–4** *and* **6** *(25 MHz, $CDCl_3$, δ_{TMS} 0.0 ppm).*

	1a		1b		1c		2a	2b[q]	2c	2d	2e	2f	2g	2h	2i[p]	2j	3	4a	4b	6
	A	B	A	B	A	B														
C-2	133.5[a]	132.6[a]	133.0[a]	132.2[a]	132.4[a]	131.5[a]	132.1	131.5	130.8	133.3	133.0	127.9[a]	127.2	128.2[a]	129.0	128.4[a]	133.5	125.2	125.1[a]	130.9
C-3	55.2	58.4	57.7[b]	60.0	53.7	57.7[b]	57.4	59.2	55.4	65.7	64.2	69.8	72.0	69.2	71.0	69.2	55.1	168.5	167.5	55.6
C-5	49.4	46.6	49.8	47.1	50.6	47.6	50.6	51.0	51.2	52.1	52.2	68.8	69.3	69.9	64.6	66.5	49.5	52.1	50.8	50.2
C-6	20.3	16.5	20.5	16.9	20.4	16.5	16.5	16.9	16.1	21.5[a]	21.4[a]	19.6	20.1	19.8	18.3[a]	18.3	20.7	19.8	19.8	18.5
C-7	113.1[c]	112.9[c]	106.9[c]	106.7[c]	109.6	109.6	112.3	105.9	108.4	112.9	109.0	112.6	105.1	107.9	111.6	107.6	113.2	128.6	125.2[a]	115.2
C-8	130.0[d]	129.7[d]	129.5	129.5	129.1[d]	129.9[d]	130.1	129.5	128.8	129.9	128.9[b]	128.7[a]	127.2	127.9[a]	126.9	126.8[a]	130.1	126.7	126.0[b]	129.9
C-9	118.0	118.0	118.4	118.4	118.2	118.2	117.9	118.5	118.0	118.1	118.1	118.3	118.6	118.4	118.8	118.7	118.2	122.4	122.4	118.6
C-10	123.8[e]	123.9[e]	120.2	120.2	120.2[e]	120.4[e]	123.7	120.3	120.0	123.8	120.1	124.3	120.7	120.9	124.3	120.7	123.9	126.7	123.6	124.1
C-11	124.3[f]	124.5[f]	121.6[f]	121.5[f]	121.7[f]	122.0[f]	124.1	121.7	121.5	124.0	121.4	125.6	122.9	123.1	124.8	122.0	124.4	132.1	130.4	124.8
C-12	116.3	116.3	110.3[g]	111.0[g]	112.6	112.6	116.1	110.3	112.3	116.2	112.4	116.3	111.6	112.8	115.8	113.2	116.4	116.9	115.2	116.0
C-13	134.5[h]	134.1[h]	134.5[h]	134.0[h]	135.0[h]	134.0[h]	134.2	134.1	133.8	135.0	135.1	134.8	135.5	134.8	134.9	134.4	134.5	138.2	139.3	134.3
C-14	167.7[i]	167.5[i]	82.4[i]	81.9[i]	129.1[d]	128.3[d]	167.5	82.0	128.2	167.6	128.1[b]	166.6	82.0	127.2[a]	165.8	127.6[a]	167.8	163.9	127.8[b]	166.5
C-15	43.3	44.1	43.9[k]	44.5[k]	128.6[j]	127.6[j]	44.2	44.6[a]	127.7	44.1	131.7	43.3	43.6	128.2	44.7	129.1	43.6	42.3	123.9	43.9
C-16	37.6	38.2	34.8[l]	35.1[l]	37.5[l]	37.9[l]	38.3	35.2	37.4	39.3	38.6	40.0	37.1	39.3	40.7	39.5	37.7	41.7	40.9	37.5
C-17	26.2	26.0	25.4	23.9	26.2	26.0	27.0	25.2	27.1	31.7	30.0	26.9	25.2	28.5	31.0	29.7	26.7	25.0	24.7	23.7
C-18	113.1	26.8	114.0	26.5	114.0	27.8	20.7	20.9	20.2	21.2[a]	22.9[a]	16.4	16.8	15.9	17.9[a]	18.3	99.4	17.5	17.1	25.4
C-19	130.0	57.3	129.5	56.7[b]	130.2	56.9[b]	44.3	44.5[a]	44.7	55.3	54.9	57.8	57.9	58.4	66.9	67.4	132.2	52.6	52.6	47.4
C-20	29.1	28.0	29.9	28.7	28.5	28.0	28.2	29.0	28.5	20.7[a]	21.4[a]	30.3	30.9	29.9	21.9	24.0	29.5	29.7	33.2	29.0
C-21	8.0	7.6	8.0	7.6	8.9	8.5	7.7	7.6	8.6	7.4	8.2	8.3	8.4	9.4	8.0	9.2	8.0	7.4	7.8	7.6
other			174.6[n]	174.2[n]	163.3[m]	163.4[m]		174.6[n]	163.2[m]		163.4[n]		173.8[n]	162.4[m]		162.7[n]			161.6[n]	
			54.3	54.3	61.7	61.7		54.3	61.5		52.1		53.8	61.9		52.5			53.1	
					14.3	14.3			14.0					14.0						

[a-l] Tentative assignment. [m] COOEt. [n] COOMe. [q] See also ref. 11. [p] $CDCl_3$ + few drops of CD_3OD.

relatively high chemical shift of C-20[13] (δ 29.1 and 29.5 ppm, respectively).

As a consequence of the γ-gauche interaction with C-18, the C-5′ signal in unit B is shifted *ca.* 4 ppm upfield relative to its value in **2a**. With C-17′, however, no upfield shift is found, which also confirms the indicated relative configuration of C-19′.

For **1b** and **1c**, ^{13}C assignments were based on the data given for **1a**. To allow comparisons, ^{13}C data for monomeric compounds **2b**[12] and **2c** are also included in Table III, together with those of the corresponding *N*-oxide derivatives **2f-h**. As to the ^{13}C assignments of the latter compounds, the definite identification of the C-18 and C-6 signals was the only problem, which was readily solved by a 2D C,H correlation measurement for **2f**. (^1H chemical shifts are given in the Experimental). Note, that while the C-18 signals show proper γ-gauche upfield shifts (~ −4 ppm) in **2f-h** due to the interaction with the N–O oxygen, interestingly, more than +3 ppm downfield shifts are found on the C-6 signals owing to the corresponding γ-*anti* effect.

In the case of *trans* isomers **2d** and **2e**, ^{13}C assignments were based on data reported earlier[13]. Assignment of *N*-oxides **2i**

Table IV Oxygen β(SCS) values (ppm) for compounds **2f-j**.

Carbon atom	2f	2g	2h	2i	2j
C-3	12.4	12.8	13.8	5.3	5.0
C-5	18.2	18.3	18.7	12.5	14.3
C-19	13.5	13.4	13.7	11.6	12.5

Table V Positional parameters of **1c**.

Atom	x/a	y/b	z/c	Atom	x/a	y/b	z/c
O(23,)	−0.0249(4)	0.4201(2)	1.5916(2)	H(3)	0.911	0.470	0.902
O(23)	0.4163(4)	0.4097(2)	0.6489(2)	H(3,)	0.132	0.428	1.210
O(24,)	−0.1532(3)	0.5107(2)	1.4962(2)	H(5b)	0.993	0.595	0.964
O(24)	0.3883(4)	0.3061(1)	0.7412(2)	H(5a)	0.968	0.616	1.075
N(1)	0.5373(4)	0.4820(2)	0.8374(2)	H(5a,)	0.213	0.508	1.081
N(1,)	0.1485(4)	0.5212(2)	1.3896(2)	H(5b,)	0.408	0.514	1.058
N(4)	0.8845(4)	0.5133(2)	1.0384(2)	H(6a)	0.692	0.652	1.040
N(4,)	0.3698(4)	0.4469(2)	1.1732(2)	H(6b)	0.781	0.681	0.947
C(2)	0.6700(5)	0.5165(2)	0.8976(3)	H(6a,)	0.464	0.603	1.176
C(2,)	0.2173(5)	0.5147(2)	1.2983(3)	H(6b,)	0.283	0.627	1.125
C(3,)	0.2380(5)	0.4409(2)	1.2474(3)	H(9)	0.390	0.711	0.892
C(3)	0.8194(5)	0.4733(2)	0.9462(3)	H(9,)	0.302	0.742	1.298
C(5,)	0.3295(5)	0.5132(3)	1.1099(3)	H(10)	0.114	0.701	0.809
C(5)	0.9156(6)	0.5929(3)	1.0161(4)	H(10,)	0.239	0.801	1.448
C(6,)	0.3448(5)	0.5893(2)	1.1651(3)	H(11)	0.016	0.588	0.739
C(6)	0.7499(6)	0.6373(2)	0.9823(4)	H(11,)	0.140	0.732	1.580
C(7,)	0.2679(5)	0.5823(2)	1.2646(3)	H(12)	0.196	0.482	0.741
C(7)	0.6316(6)	0.5890(2)	0.9149(3)	H(12,)	0.080	0.604	1.564
C(8)	0.4616(6)	0.6026(2)	0.8651(3)	H(15)	0.678	0.312	0.854
C(8,)	0.2313(5)	0.6354(2)	1.3409(3)	H(15,)	0.111	0.345	1.443
C(9)	0.3524(7)	0.6649(3)	0.8614(4)	H(17a)	0.649	0.342	1.083
C(9,)	0.2587(6)	0.7137(2)	1.3515(4)	H(17b)	0.523	0.396	1.022
C(10)	0.1887(7)	0.6586(3)	0.8130(4)	H(17a,)	0.483	0.337	1.411
C(10,)	0.2218(6)	0.7483(2)	1.4403(4)	H(17b,)	0.477	0.424	1.409
C(11)	0.1314(6)	0.5910(3)	0.7700(4)	H(18a,)	0.702	0.382	1.319
C(11,)	0.1596(7)	0.7075(3)	1.5191(4)	H(18b,)	0.572	0.335	1.250
C(12)	0.2363(6)	0.5282(3)	0.7712(3)	H(19,)	0.582	0.490	1.259
C(12,)	0.1252(6)	0.6311(2)	1.5102(3)	H(20b)	0.981	0.361	1.057
C(13,)	0.1599(5)	0.5961(2)	1.4200(3)	H(20a)	0.886	0.293	1.005
C(13)	0.4038(6)	0.5351(2)	0.8189(3)	H(20a,)	0.283	0.302	1.209
C(14)	0.5480(5)	0.4048(2)	0.8167(3)	H(20b,)	0.102	0.301	1.253
C(14,)	0.0976(5)	0.4551(2)	1.4396(3)	H(21a)	1.155	0.308	0.942
C(15)	0.6619(5)	0.3622(2)	0.8734(3)	H(21c)	1.009	0.321	0.856
C(15,)	0.1503(6)	0.3883(2)	1.4090(3)	H(21b)	1.104	0.389	0.908
C(16)	0.7651(5)	0.3918(2)	0.9670(3)	H(21a,)	0.242	0.189	1.286
C(16,)	0.2673(5)	0.3763(2)	1.3249(3)	H(21b,)	0.215	0.229	1.387
C(17,)	0.4604(5)	0.3794(2)	1.3695(3)	H(21c,)	0.396	0.230	1.343
C(17)	0.6386(6)	0.3896(2)	1.0516(3)	H(25a)	0.185	0.300	0.639
C(18,)	0.5862(6)	0.3798(2)	1.2884(3)	H(25b)	0.353	0.266	0.601
C(18)	0.6693(5)	0.4481(2)	1.1308(3)	H(25a,)	−0.338	0.470	1.578
C(19,)	0.5550(5)	0.4471(2)	1,2180(3)	H(25b,)	−0.236	0.536	1.631
C(19)	0.7817(5)	0.5046(2)	1.1222(3)	H(26a)	0.166	0.171	0.640
C(20)	0.9257(6)	0.3425(3)	0.9951(4)	H(26b)	0.166	0.201	0.749
C(20,)	0.2241(6)	0.3019(2)	1.2694(3)	H(26c)	0.335	0.167	0.711
C(21,)	0.2740(7)	0.2308(3)	1.3264(4)	H(26a,)	−0.510	0.576	1.571
C(21)	1.0609(8)	0.3401(4)	0.9179(5)	H(26b,)	−0.472	0.552	1.463
C(22,)	−0.0274(5)	0.4600(2)	1.5185(3)	H(26c,)	−0.370	0.618	1.515
C(22)	0.4439(6)	0.3751(2)	0.7253(3)				
C(25)	0.2855(7)	0.2706(3)	0.6576(4)				
C(25,)	−0.2867(6)	0.5172(3)	1.5682(4)				
C(26)	0.2337(7)	0.1953(3)	0.6924(4)				
C(26,)	−0.4217(7)	0.5706(3)	1.5255(5)				

and **2j** was straightforward. The C-6 and C-18 signals are shifted *ca.* 3 ppm upfield owing to the γ-gauche interactions with the N–O oxygen. The β(SCS) (substituent-induced chemical shift) values of the N–O oxygen in compounds **2i-j** show characteristic differences (Table IV), depending on the axial (Δδ 11.6–14.3 ppm) or equatorial (Δδ 18.2–18.7 ppm) position of the oxygen in the corresponding ring. In compounds **2i** and **2j**, however, the deshielding effect on C-3 is strikingly smaller (Δδ 5.0–5.3 ppm).

Both structure elucidations and ^{13}C assignments for iminium salts **4a** and **4b** were based on recently reported data[14]. In the case of **4b**, an unambiguous differentiation of the not readily assignable C-20–C-17; C-18–C-6 and C-10–C-15 signal pairs was also achieved by recording a C,H correlation map (25/100 MHz) and by considering the corresponding ^1H chemical shift relations (see Experimental).

For compound **6**, the ^{13}C and ^1H data justify the C-19 position of the CN group in a self-explanatory manner. Assignment of the H-19 signal was unambiguously confirmed by a 2D hetero-correlation measurement (see Experimental). The small couplings of H-19 [$J(H_e\text{-}19\text{–}H_a\text{-}18)$ 4.9 Hz, $J(H_e\text{-}19\text{–}H_e\text{-}18)$ 2.3 Hz] establish the axial (β) position of the CN group. This conclusion is supported by the ~0.6 ppm downfield shift of the H_a-17 and H_a-6 signals (*cf.* **2a**), owing to the anisotropic effect of the axial CN group, and also by the γ-gauche effect found on the C-17 carbon signal (– 3.3 ppm).

2. *X-ray structure determination of* **1c**

Crystals of **1c** are monoclinic (M_w = 695.89) space group $P2_1$, a = 7.686(1), b = 17.828(5), c = 13.287(2) Å, β = 94.37(1)°, V = 1815.3(10) Å^3, Z = 2, d_c = 1.273 g/cm^3, $F(000)$ = 742. Intensities were measured from a crystal of 0.15 × 0.18 × 0.30 mm^3 dimensions with an Enraf-Nonius CAD-4 diffractometer at room temperature (295 ± 1 °K) using graphite monochromated CuK_α radiation (λ = 1.54184 Å) θ/2θ mode, 1.5 < θ < 75.0°, scan width (θ): (0.60 + 0.14tgθ).

The solution of the phase problems (MULTAN)[15] and full-matrix refinement of the atomic parameters were based on 3087 reflections with $I > 1.5\sigma(I)$ (from counting statistics). In the course of isotropic refinement of the positional parameters of non-hydrogen atoms, an empirical absorption correction (μ = 6.1 cm^{-1}) was calculated with the programme DIFABS[16]; minimum and maximum absorption corrections 0.546 and 1.616. Refinement of scale factor, positional and anisotropic thermal parameters of non-hydrogen atoms resulted in R = 0.055, R_w = 0.058, R_{tot} = 0.066, S = 3.76. The largest parameters shift/error in the last cycle of refinement was 0.57; maximum and minimum peak heights in final Δρ map 0.27 e/Å^3. Positions of H atoms were generated from assumed geometries; their positions were taken into account without refinement in the structure factor calculations with isotropic temperature factors ($B_{iH} = B_{iC} + 1$ Å^2). Positional parameters are given in Table V. A drawing of the structure of **1c** showing atomic numbering (whilst the hydrogens are deliberately omitted for clarity) substantiates a dimeric structure (indicated as unit A and B) via a C-18–C-19′ single bond of 1.507(6) Å, which, as expected, assumes an α-equatorial position [C-18–C-19′–C-18′–C-17′ 176.2(8)°] to the D ring of unit B. The saturated D ring in unit B possesses chair conformation while in unit A it retains a transitional form between a half-chair ($^3H_{16}$) and envelope (^3E) in accordance with the double bond between C-18 and C-19 [1.336(6) Å]. The puckering of the C and E rings is unaffected by the change in that of ring D. In both A and B units, ring C has an ^4E envelope shape while ring E assumes a skew (1,3-diplanar) conformation.

Experimental

Reagents and solvents were used as obtained from the supplier. In preparative column and TLC chromatography, MERCK Kieselgel 60 was used. The optical rotations were recorded in chloroform at 25 ± 2°C. IR spectra were recorded on a Specord IR 75 spectrometer using KBr pellets or film. The UV absorption spectra were recorded on a UV Specortd UV-VIS spectrometer; the spectra were measured in ethanol.

All the NMR spectra were recorded in the PFT mode, with internal deuterium lock at ambient temperature (298 K), on Bruker WH-400/DS, Bruker WM-250, Bruker WH-360, Varian XL-400 and Jeol FX-100 spectrometers. The ^1H chemical shifts and coupling constants were calculated as first-order spectra at 400 MHz. Two-dimensional experiments were recorded by using the standard spectrometer software packages. Mass spectra were recorded on an AEI-MS-902 (70 eV, direct insertion) mass spectrometer. M.p. s are uncorrected.

Preparation of N-*oxides* (**2f-j**)

(–)-Vincamone N-*oxide* (**2f**). To a solution of (–)-Vincamone **2a** (29.4 g, 0.1 mol) in chloroform (700 ml), a solution of *m*-chloroperbenzoic acid (*m*-CPBA) (Fluka, 25.8 g, 0.15 mol) in chloroform (100 ml) was added and the mixture stirred at room temp. for 1 h. The reaction mixture was shaken with 120 ml 10% NaOH solution. The aqueous solution was extracted with chloroform (2 × 50 ml) and the combined organic layers were washed with water (2 × 50 ml) and dried (Na_2SO_4). The filtrate was evaporated *in vacuo* and the residue (29.6 g) was crystallized from ether (50 ml) to yield 28.3 g of **2f** (91.3%); m.p. 220–222°C; $[\alpha]_D$ – 61.9 (*c* 0.2, $CHCl_3$). Anal. $C_{19}H_{22}O_2N_2$ (310.38) calcd.: C 73.52, H 7.14, N 9.03; found: C 73.49, H 7.22, N 8.97%. UV (EtOH) λ_{max}/nm (lgε): 202 (4.44), 239 (4.33), 263 (4.09), 291 (4.87), 298 (4.87). IR (KBr): 1720, 1630, 1140 cm^{-1}. MS *m/e* (%): 310 (M$^+$, 57), 294 (M – 16,100), 293 (96), 291 (11), 265 (28), 263 (10), 251 (8), 237 (22), 236 (14), 224 (61), 222 (11), 209 (7), 196 (7), 194 (8), 180 (20), 167 (20). ^1H NMR (100 MHz, $CDCl_3$) δ: 1.00 (t, 3H, $-CH_2\underline{CH}_3$), 2.39 (q, 2H, $-\underline{CH}_2CH_3$), 2.82 (d, 1H, 15-H), 2.50 (d, 1H, 15-H), 0.9–1.7 (m, 3H, 17-H_2 + 18-H_e), 2.2–3.4 (m, 5H, 19-H_2 + 6-H_2 + 18-H_a), 3.6–4.2 (m, 2H, 5-H_2), 4.48 (s, 1H, 3-H), 7.20–7.35 (m, 3H, 9-H, 10-H, 11-H), 8.35 (m, 1H, 12-H).

2g-j were prepared according to the above procedure.

(–)-Vincamine N-*oxide* (**2g**). Yield 84.8%; m.p. 275–276°C (from ethyl acetate) (lit.[17] 280°C); $[\alpha]_D$ – 8.9 (*c* 1, $CHCl_3$) (lit.[17] – 2 ± 5). Anal. $C_{21}H_{26}O_4N_2$ (370.43) calcd.: C 68.09, H 7.07, N 7.56; found: C 67.95, H 7.13, N 7.49. IR (KBr): 1750, 3450, 960 cm^{-1}. MS *m/e* (%): 370 (M$^+$, 24), 354 (38), 353 (28), 337 (2). ^1H NMR (100 MHz, $CDCl_3$) δ: 1.00 (t, 3H, $-CH_2\underline{CH}_3$), 4.34 (s, 1H, 3-H), 2.27 (s, 2H, 15-H), 3.78 (s, 3H, $-COO\underline{CH}_3$), 7.44 (m, 1H, 9-H), 7.00–7.30 (m, 3H, 10-H, 11-H, 12-H), 1.15 (m, 14H, skeletal + $-\underline{CH}_2CH_3$).

(+)-Apovincaminic acid N-*oxide ethyl ester* (**2h**). Yield 96.1%; m.p. 98–99°C (from a mixture of ethyl acetate/petroleum ether 3/7); $[\alpha]_D$ + 111.6 (*c* 0.2, $CHCl_3$). Anal. $C_{22}H_{26}O_3N_2$ (366.44) calcd.: C 72.10, H 7.15, N 7.65; found: 72.18, H 7.04, N 7.66%. UV (EtOH) λ_{max}/nm (lgε): 204 (4.39), 225 (4.46), 269 (4.09), 313 (3.94). IR (KBr): 1700, 1610 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ: 1.10 (t, 3H, $-CH_2\underline{CH}_3$), 2.30 (q, 2H, $-\underline{CH}_2CH_3$), 4.65 (s, 1H, 3-H), 6.05 (s, 1H, 15-H), 7.45 (m, 1H, 9-H), 7.10–7.30 (m, 3H, 9-H, 10-H, 11-H), 1.20–4.20 (m, 10H, skeletal).

(±)-3-Epieburnamenin-14(15H)-one N-*oxide* (**2i**). Yield 80%; m.p. 127–131°C (from ethyl acetate). Anal. $C_{19}H_{22}O_2N_2$ (310.38) calcd.: C 73.52, H 7.14, N 9.03; found: C 73.60, H 7.28, N 8.99%. IR (KBr): 1700, 1650, 1640 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ: 0.70 (t, 3H, $-CH_2\underline{CH}_3$), 2.39 (d, 1H, 15-H), 2.95 (d, 1H, 15-H), 4.61 (s, 1H, 3-H), 1.2–4.8 (m, 12H, skeletal + $-\underline{CH}_2CH_3$). 7.2–7.5 (m, 3H, 9-H, 10-H, 11-H), 8.30 (m, 1H, 12-H).

(–)-14-(Methoxycarbonyl)-(3β,16α)-eburnamenine N-*oxide* (**2j**). Yield 74%; m.p. 125–128°C (from ether). $[\alpha]_D$ – 141.2 (*c* 0.2, $CHCl_3$).

Anal. $C_{21}H_{24}O_3N_2$ (352.42) calcd.: C 71.57, H 6.86, N 7.95; found: C 71.34, H 6.95, N 8.01. UV (EtOH) λ_{max}/nm (lgε): 205 (4.39), 227 (4.33), 270 (3.97), 312 (3.82). IR (KBr): 1720, 1650, 1600 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ: 0.70 (t, 3H, $-CH_2CH_3$), 3.90 (s, 3H, $-COOCH_3$), 4.02 (s, 1H, 3-H), 6.17 (s, 1H, 15-H), 7.05–7.5 (m, 4H, 9-H, 10-H, 11-H, 12-H), 1.3–3.9 (m, 12H, skeletal + $-CH_2CH_3$).

Preparation of dimers **1a-c**

Route A: reaction of N*-oxides with acetic anhydride*

1a. **2f** (12.41 g, 40 mmol) was dissolved in acetic anhydride (50 ml. 0.53 mol) and the mixture stirred at room temp. for 24 h. The precipitated crystals were filtered off, washed with ether (2 × 10 ml) and dried to give **1a** (6.14 g, 52.5%). For physical data see ref. 2.

1b. **2g** (52 g, 0.14 mol) was dissolved in acetic anhydride (500 ml, 5.3 mol) and the mixture stirred at room temp. for 24 h. The reaction mixture was poured into 400 g of broken ice and 3 l of ethyl acetate were added. The mixture was alkalized to pH 8 by adding concentrated aqueous amonium hydroxide solution (0.9 l) while stirring. The organic layer was separated and washed with water (7 × 100 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue (46.5 g) was crystallized rom methanol (120 ml) to give 22 g of **1b** (44.4%). For physical data see ref. 2.

1c. **2h** (3 g, 8.2 mmol) was dissolved in acetic anhydride (10 ml, 0.105 mol) and the mixture stirred at room temp. for 24 h. The reaction mixture was poured into 60 g of broken ice and 200 ml of ethyl acetate was added. The mixture was alkalized to pH 8 by adding concentrated aqueous ammonium hydroxide solution (16 ml) while stirring. The organic layer was separated and washed with water (4 × 20 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue (2.4 g) was chromatographed on silica (eluent: cyclohexane/ethyl acetate 7/3). The collected eluates were evaporated *in vacuo* and the residue (1.02 g) was crystallized from ethanol (15 ml) to afford **1c** (0.8 g, 28%). For physical data see: ref. 2.

Route B: water elimination and transesterification of **1b**

1d. A mixture containing **1b** (14.03 g, 20 mmol) and *p*-toluenesulphonic acid monohydrate (20.12 g, 0.105 mol) in benzene (1000 ml) was refluxed using a water-separating device for 4 h and then cooled. After adding 200 ml of water, the pH was adjusted to 8 by using concentrated aqueous ammonium hydroxide solution (30 ml). After extraction, the benzene phase was washed with water (3 × 100 ml), dried (Na_2SO_4), filtered and the filtrate evaporated to dryness under reduced pressure. The residue was crystallized from methanol (100 ml) to give a crude product (11.1 g, 80.6%), which was dissolved in chloroform (400 ml), cleared with silica (50 g), filtered and the filtrate evaporated under reduced pressure. The residue was crystallized from methanol (50 ml) to afford **1d** (6.8 g, 49.4%); m.p. 178–190°C; $[\alpha]_D$ −224.3 (*c* 0.2, $CHCl_3$). Anal. $C_{42}H_{44}O_4N_4$ (668.80) calcd.: C 75.42, H 6.63, N 8.38; found: C 75.39, H 6.65, N 8.29%. MS *m/e* (%): 668 (M^+, 17), 640 (1.5), 639 (1.2), 637 (1), 610 (1.4), 609 (1.3), 373 (47), 360 (3.8), 343 (4.7), 335 (49), 334 (M/2, 14), 280 (10), 266 (100), 251 (11), 135 (3.1), 71 (7.6), 57 (7.1), 50 (16), 44 (9). ^1H NMR (100 MHz, $CDCl_3$) δ: 0.94 (t, 3H, $-CH_2CH_3$), 1.07 (t, 3H, $-CH_2CH_3$), 4.28 (s, 1H, 3-H), 3.9 (s, 1H, 3-H, overlap), 3.95 (s, 3H, $-COOCH_3$), 3.90 (s, 1H, $-COOCH_3$), 6.40 (s, 1H, 15-H), 6.12 (s, 1H, 15-H), 5.84 (d, *J* 1.5 Hz, 1H, 19-H in part A), 7.00–7.30 (m, 6H, 10-H, 11-H, 12-H), 7.44 (m, 2H, 9-H), 1.20–3.80 (m, 20H, skeletal + $-CH_2CH_3$).

1.37 g (2 mmol) of this substance and potassium *tert*-butoxide (0.01 g) in anhydrous ethanol (100 ml) was refluxed for 3 h. After cooling the solution to room temp., the precipitated crystals were filtered off and washed with ethanol (2 × 10 ml) to yield **1c** (1.2 g, 79.5%).

Route C: reaction of N*-oxide* **2h** *with* $K_2Cr_2O_7$

1c. **2h** (1.46 g, 4 mmol) was dissolved in water (100 ml) at 75–80°C. A solution of $K_2Cr_2O_7$ (1.2 g, 4 mmol) in water (5 ml) was added and the mixture stirred for 5 min. After cooling to room temp., 30 ml saturated $NaHCO_3$ solution was added under stirring and the mixture was extracted with ethyl acetate (5 × 50 ml). The combined organic phase was washed with water (3 × 10 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue (1.3 g) was chromatographed on silica (eluent: cyclohexane/ethyl acetate 99/1, 200 ml; 9/1, 100 ml; 7/3, 100 ml). The solvent was evaporated under reduced pressure and the residue was crystallized from ethanol (10 ml) to give **1c** (0.62 g, 44.9%).

Route D: reaction of N*-oxide* **2h** *with trifluoracetic anhydride*

1c. **2h** (0.36 g, 1 mmol) was dissolved in dry methylene chloride (5 ml), cooled to −20°C and trifluoracetic anhydride (Aldrich, 0.3 ml, 2.1 mmol) was added dropwise over a period of 3 min. Stirring was continued at −20°C for 1 h and the same amount of trifluoroacetic anhydride was then added. The mixture was evaporated under reduced pressures and the residue dissolved in a mixture of hot water (5 ml) and ethanol (2 ml). The solvent was then alkalized to pH 8 by adding a concentrated aqueous ammonium hydroxide solution. The precipitated crystals were filtered, washed with water and dried to give a crude product (190 mg) which was chromatographed by preparative TLC on silica (20 × 20 cm, 1.5 mm thick layer, using a 9/1 mixtureof cyclohexane and ethyl acetate) to afford **1c** (90 mg, 23%).

Route E: reaction of enamine **3** *with acetic acid*

3 (292 mg, 1 mmol) was dissolved in glacial acetic acid (10 ml) and stirred at 80°C for 1½ h. After removal of the acetic acid *in vacuo*, the residue was dissolved in a mixture of ethyl acetate/saturated $NaHCO_3$ solution (50/20 ml). The organic layer was separated and washed with water (2 × 25 ml), dried (Na_2SO_4) and filtered. The solution was then concentrated under reduced pressure to 5 ml ands allowed to crystallize to afford **1a** (148 mg, 50.7%).

Preparation of enamine **3**

(−)-18,19-Dehydro-(3α,16α)-eburnamenin-14(15H)-one (**3**). **2f** (1.24 g, 4 mol) was dissolved in water (35 ml) at 65–70°C. A solution of $K_2Cr_2O_7$ (1.2 g, 4 mmol) in water (5 ml) was then added and the mixture stirred for 5 min at 75–80°C. After cooling to room temp., 30 ml saturated $NaHCO_3$ solution was added under stirring and the mixture was extracted with ethyl acetate (5 × 10 ml). The combined organic layer was washed with water (3 × 10 ml), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue (0.9 g) was crystallized from methanol (20 ml) to give **3** (44.8%); m.p. 153–154°C (lit.[4] 153°C). $[\alpha]_D$ −102.8 (*c* 0.2, $CHCl_3$). $C_{19}H_{20}ON_2$ (292.37) calcd.: C 78.05, H 6.90, N 9.58; found: C 78.12, H 6.73, N 9.32%. MS *m/e* (%): 292 (M^+, 78), 291 (31), 277 (2.4), 264 (9), 263 (22), 261 (5.3), 235 (5.4), 224 (M-68, 100), 196 (4.8), 180 (9.6), 168 (14), 167 (18). ^1H and ^{13}C NMR data see Tables I–III.

Preparation of iminium salts **4a-b**

(±)-3,4-Dehydroeburnamenin-14(15H)-one (**4a**). **2i** (0.31 g, 1 mmol) was dissolved in dry methylene chloride (15 ml), cooled below 0°C and trifluoroacetic anhydride (0.6 ml, 4.2 mmol) was added dropwise. Stirring was continued at 0°C for 1 h and at room temp. for 24 h. After evaporation of the solvent under reduced pressure (bath temp. 20°C), the oily iminium compound **4a** was obtained in quantitative yield. ^1H NMR (100 MHz, $CDCl_3$) δ: 0.97 (t, 3H, $-CH_2CH_3$), 1.4–2.3 (m, 6H, $-CH_2CH_3$ + 17-H_2 + 18-H_2), 3.01 (d, 1H, 15-H), 3.22 (d, 1H, 15-H), 3.2–3.5 (m, 2H, 6-H_2), 3.8–4.6 (m, 4H, 5-H_2 + 19-H_2), 7.1–7.9 (m, 3H, 9-H, 10-H, 11-H), 8.36 (dd, 1H, 12-H).

Following the above procedure compound **4b** was prepared from **2j**.

(−)-3,4-Dehydro-14-(methoxycarbonyl)-(16α)-eburnamenine **4b**. $[\alpha]_D$ −398.9 (*c* 0.2, $CHCl_3$). UV (EtOH) λ_{max}/nm (lgε): 210 (4.53), 238 (4.27), 260 (4.09), 358 (4.20). IR (film): 1800, 1740, 1660, 1590 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ: 0.83 (t, 3H, $-CH_2CH_3$), 1.90 (q, 2H, $-CH_2CH_3$), 1.9–2.5 (m, 4H, 17-H_2 + 18-H_2), 3.35 (m, 2H, 6-H_2), 3.99 (s, 3H, $-COOCH_3$), 3.55–4.35 (m, 4H, 5-H_2 + 19-H_2), 6.32 (s, 1H, 15-H), 7.30 (t, 1H, 10-H), 7.66 (d, 1H, 9-H), 7.40–7.56 (m, 2H, 11-H, 12-H).

Cyanide trapping of iminium salt **5**

(+)-19-Cyano-(3α,16α,19β)-eburnamenine-14(15H)-one (**6**). To a solution of **2f** (0.44 g, 1.5 mmol) in dry methylene chloride (15 ml) at 0°C, trifluoroacetic anhydride (1 ml, 7 mmol) was added and the reaction mixture was stirred at room temp. for 24 h. Solvent

and excess reagent were removed by rotatory evaporation without heating and methylene chloride (20 ml) added, followed, at 0 °C, by potassium cyanide (0.5 g, 7.6 mmol) in water (1 ml). The pH was immediately adjusted to 4 by trifluoroacetic acid addition and the mixture stirred at room temp. for 1 h. Saturated $NaHCO_3$ solution was added to pH 8 and the layers separated. The organic layer was washed with water (2 × 25 ml), dried (Na_2SO_4), filtered and evaporated to give a brown oil, which was crystallized from methanol (10 ml) to yield **6** (0.16 g, 33.5%); m.p. 194–198 °C; $[\alpha]_D$ + 56.9 (*c* 0.2, $CHCl_3$). $C_{20}H_{21}ON_3$ (319.39) calcd.: C 75.21, H 6.63, H 13.16; found: C 75.09, H 6.57, N 12.09%. IR (KBr): 1690, 1610, 1420, 1430 cm^{-1}. MS *m/e* (%): 319 (M^+, 100), 318 (23), 292 (26), 291 (26), 290 (47), 263 (15), 262 (16), 224 (57), 209 (8.1), 180 (12), 168 (13), 167 (15), 159.5 (6.5). ^1H NMR (250 MHz, $CDCl_3$) δ: 0.95 (t, 3H, 21-H_3), 1.4–1.7 (m, 3H, 20-H_x + 17-H_a + 17-H_e), 1.78 (dq, 1H, 18-H_e, J_{gem} 14.0 Hz, $J_{18e,17e} \sim J_{18e,19e}$ 2.3 Hz, $J_{18e,17a}$ 3.2 Hz), 2.05 (dq, 1H, 20-H_y), 2.15 (m, 1H, 18-H_a), 2.59 (dm, 1H, 6-H_e), 2.7 (s, 2H, 15-H_2), 3.35–3.6 (m, 3H, 6-H_a, 5-H_a, 5-H_e), 3.97 (dd, 1H, 19-H_e, $J_{19e,18a}$ 4.9 Hz, $J_{19e,18e}$ 2.3 Hz), 4.07 (t, 1H, 3-H, *J* ~ 1.7 Hz), 7.28 (td, 1H, 10-H), 7.35 (td, 1H, 11-H), 7.44 (dd, 1H, 9-H), 8.35 (dd, 1H, 12-H).

Acknowledgements

The authors wish to thank Dr. *J. Tamás* and Miss *M. Mák* for mass spectra and Dr. *L. Párkányi* and Mr. *Cs. Kertész* for their valuable assistance in the X-ray structure determination.

They are grateful to Prof. *G. Bodenhausen* (Lausanne, Switzerland), to Dr. *I. Pelczer* and *Dr. L. Radics* for some valuable NMR spectra and also to the OTKA program of the Hungarian Academy of Sciences for financial support. One of us (G.T.) thanks the Natural Sciences and Engineering Research Council of Canada for a visiting fellowship (University of Alberta, Edmonton, Alberta, Canada).

Special thanks are due to Mrs. *K. Welker* for technical assistance.

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E-GYŰRŰBEN MÓDOSÍTOTT VINCA-ALKALOIDOK

Tetrahedron Vol. 48, No. 23, pp. 4999-5008, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Synthesis of Vinca Alkaloids and Related Compounds LX[1]. A Simple Transformation of Apovincamine into Vincamine**

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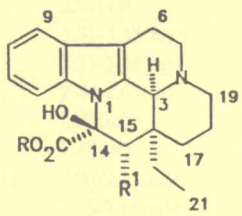
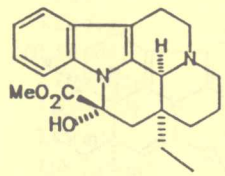
(*Received in UK 9 December* 1991)

Abstract: *The 15α-chloro-vincamine derivative* **2** *was prepared and proved to be key intermediate of a two-step transformation of apovincamine into vincamine. The structure of* **2** *was established via detailed NMR and X-ray investigations.*

The transformation of (+)-vincamine (**1**) or (-)-epivincamine (**5**) into (+)-apovincamine (**3**) can be achieved in a straightforward way via various methods[2]. The reverse process, however, requires more delicacy, and up until now only three such methods have been published[3], all of them more or less tedious in practice.



	R	R^1
1	Me	H
2	Me	Cl
6	Et	Cl



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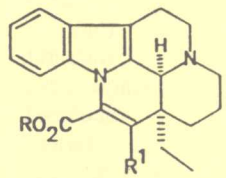


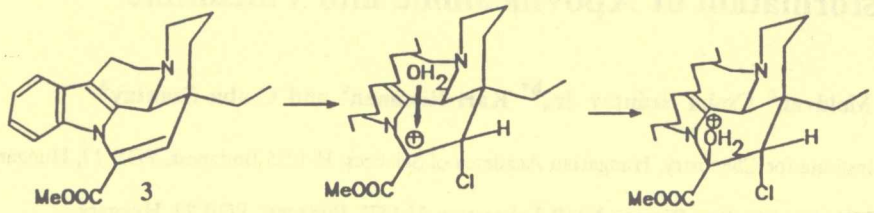
	R	R^1
3	Me	H
4	Me	Cl
7	Et	H

Since apovincaminic acid esters are easily available through total synthesis[4], their efficient conversion into (+)-vincamine is a goal of considerable attraction. Here we describe a convenient, two-step method for the transformation of **3** into **1**, involving addition of the elements of HOCl and subsequent catalytic reduction.

Lewin and Poisson[3b] reported that when attempting hypohalogenide addition onto **3** in aqueous solution, they obtained a mixture of different products which was not studied further. We have found, however, that when (+)-apovincamine (**3**) was dissolved in concentrated hydrochloric acid and treated with aqueous solution of sodium nitrite, the crystalline HCl salt of the 15α-chloro derivative **2** had formed after 15-20 min. in 76 % yield with no other isomers being isolable or detectable.

** *We dedicate this paper to Professor Gábor Fodor on the occasion of his 75th birthday.*

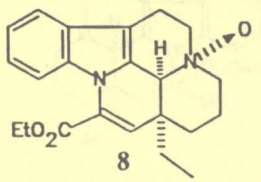
The very high regio- and stereoselectivity of the reaction is remarkable. Assuming an HOCl addition one would rationalize this selectivity by following the usual pattern of the generally accepted mechanism:



Accordingly, in the first step the chloro cation attacks at C(15) and after formation of a carbocation, in the second step a molecule of water attacks the quasi-planar cation from the β face. Selective formation of the vincamine-type configuration at C(14) may be attributed to an anomeric effect[5]. Finally, deprotonation gives rise to **2**. However, some experimental observations seem to contradict this reaction sequence.

From the foregoing mechanism one may conclude that using HOCl as reactant instead of the HCl + $NaNO_2$ system would be appropriate, and should afford the same result (**3** → **2**). However, when HOCl was applied as a reaction partner in acidic medium, or a combination of hydrochloric acid and an oxidizing agent (e.g. H_2O_2) was used, no halohydrin **2** could be isolated, only polyhalogenated products were detected. Consequently it is quite possible that a different reaction sequence is involved when the HCl + $NaNO_2$ system is applied.

Investigating further the said transformation, another, unique procedure for obtaining 15α-chloro-vincamines was found. When the N-oxide (**8**)[6] was reacted with thionyl chloride in benzene for 24 h at room temperature, **6** was obtained in 30 % yield after work up. The presence of the N-oxide function proved to be imperative for this process. It is worthy of note that **8** is stable in cc. hydrochloric acid. Taking account of the above experimental results, it is clear that further studies of the reaction sequence are required for putting forward a plausible mechanism with regard to the highly selective chlorohydrine formation. The investigation of the reaction conditions relating to the formation of the 15α-chloro-vincamines will be further pursued.



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It is noted that (+)-vincamine (**1**) also gave the chloro derivative **2** (80 %) when **1** was reacted according to the above procedure (HCl + $NaNO_2$). With this route the first step probably involves dehydration of **1** into **3**. This assumption is substantiated by the fact that under the same reaction conditions 14-epivincamine (**5**) also converted into **2**. Upon carrying out the above reaction without sodium nitrite, only dehydration (**1** → **3**) occurred.

The chloro compound **2** can be conveniently transformed into the appropriate dehalogenated derivative (**1**) by hydrogenolysis (H_2, Pd/C, r.t., in MeOH) in 75-85 % yield and without the formation of the C-14 epimer **5**.

Although the stereoelectronic requirements for water elimination in **2** are clearly not ideal, its treatment with acid (p-$MeSO_3H$, benzene, reflux, 2h) afforded the unsaturated chloro derivative (**4**) in 85 % yield. The easy dehydration of **2** into **4** could be thought of as being indicative of an antiperiplanar arrangement for C(14)-OH and H-15, as opposed to the found *cis* relationship between them. This observation added special significance to the unambiguous verification of the stereostructure of **2** as detailed below.

When starting from 2, many unusual reactions have been observed which will be presented in a subsequent paper.

Structure determinations.

NMR spectroscopy. The structures of compounds **2** and **4** were first deduced from detailed ^1H and ^{13}C NMR studies. ^1H and ^{13}C chemical shifts are collected in Table 1 and Table 2, respectively. For the sake of completeness and comparison, we have also included the relevant ^1H data for **1**, **3**, and **5** in Table 1 and the ^{13}C assignments for compounds **1** and **3** in Table 2. For each of these compounds the assignments presented here were secured by the concerted use of 2D ^1H-^1H and ^{13}C-^1H correlation experiments and homonuclear 1D NOE measurements (see also the $^{13}C\{^1H\}$ NOEs for **2** in Table 2). It is noted that ^{13}C assignments for **1** and **5** were reported earlier[7], and for **7** and **8** ^{13}C chemical shifts are given in ref. 6. Elaborate NMR data for various indole compounds containing the eburnane skeleton have been published before[8]. However, our computer-aided literature search failed to locate any detailed high-field ^1H NMR assignments, such as given in Table 1, for the known compounds **1**, **3** and **2**.[9] Some of the most informative $^1H\{^1H\}$ NOEs for compounds **1** - **4** are listed in Table 3.

For the 15α-chloro derivative **2** several pieces of evidence readily establish the configuration at C(15): Most importantly, irradiation of H-15 gave an NOE into H_e-17, while no NOE connection was detected between H-15 and H-3, which assignes a β position to H-15 (see Fig. 2 for a perspective view of **2**). As compared to vincamine (**1**), in **2** C(3) is shifted upfield by δ -2.8 ppm as a result of a C(15)α-Cl ↔ C(3)H γ_{gauche} steric interaction. Futhermore, the C(15)α-Cl exerts a γ_{gauche} upfield shift of -4.4 ppm on C(20) and a γ_{anti} effect on C(17) ($\Delta\delta$ = -1.3 ppm). It should be noted, however, that the $\delta_{C(3)}$ and $\delta_{C(17)}$ values may also be affected by γ-steric interactions with the C(21)H_3 group. For this reason, the

Table 1. ^1H Chemical Shifts for Compounds **1** - **5**.

Proton	1	2	3	4	5
H-3	3.91(s)[d]	4.18(s)[d]	4.12(s)[d]	4.40(s)[d]	3.78(s)[d]
H_a-5	3.31-3.38(m)[a]	3.29-3.41(m)[a]	3.22(ddd)	3.17(ddd)	3.17(ddd)
H_e-5	3.31-3.38(m)[a]	3.29-3.41(m)[a]	3.33(ddd)	3.28(ddd)	3.26(ddd)
Hα-6	2.44-2.64(m)[b]	2.56-2.68(m)[b]	2.47(dddd)	2.43(dddd)	2.45-2.60(m)[a]
Hβ-6	2.98(m)	2.99(m)	3.00(dddd)	2.91(dddd)	2.96(dddd)
H-9	7.48(m)	7.50(m)	7.45(m)	7.38(m)	7.46(m)
H-10,11	7.06-7.15(m)[c]	7.12-7.19(m)	7.08-7.19(m)	7.04-7.12(m)	7.07-7.15(m)
H-12	7.06-7.15(m)[c]	7.03(m)	7.22(m)	6.91(m)	7.30(m)
H-15	2.22(d)[Hα-15]	-	6.13(s)	-	1.98(d)[Hα-15]
	2.11(d)[Hβ-15]	4.30(s)[Hβ-15]		7.38(m)	2.57(d)[Hβ-15]
H_a-17	1.68(m)	1.68(m)	0.99(td)	1.19(td)	1.17-1.35(m)[b]
H_e-17	1.47(m)	1.56(m)	1.49(ddd)	1.65(m)	1.17-1.35(m)[b]
H_a-18	1.72(m)	1.80(m)	1.69(ddddd)	1.72(m)	1.67(m)
H_e-18	1.38(m)	1.37(m)	1.38(ddddd)	1.41(m)	1.17-1.35(m)[b]
H_a-19	2.44-2.64(m)[b]	2.44(m)	2.57-2.64(m)[a]	2.50-2.66(m)[a]	2.45-2.60(m)[a]
H_e-19	2.44-2.64(m)[b]	2.56-2.68(m)[b]	2.57-2.64(m)[a]	2.50-2.66(m)[a]	2.45-2.60(m)[a]
H_x-20	1.45(dq)	1.84(dq)	1.80-2.00(m)[b]	2.26(dq)	1.38(dq)
H_y-20	2.24(dq)	2.48(dq)	1.80-2.00(m)[b]	1.68(dq)	2.12(dq)
H_3-21	0.90(t)	0.93(t)	1.00(t)	0.98(t)	0.87(t)
OMe	3.82(s)	3.85(s)	3.93(s)	3.96(s)	3.71(s)
OH	4.66(s)	4.56(s)	-	-	4.40(s)

[a,b,c] Like superscripts denote overlapping signals. [d] Broadened by long-range couplings to H_2-6 (homoallylic) and H_e-17,19 ('W').

Table 2. ^{13}C Chemical Shifts for Compounds 1 - 4.

Carbon	1	2	3	4
C(2)	131.4	129.9	130.9	128.6[a]
C(3)	59.1	56.3	55.6	53.0
C(5)	50.9	50.8	51.3	51.8
C(6)	16.8	16.8	16.2	16.2
C(7)	105.9	106.7	108.6	108.8
C(8)	129.0	129.0	129.0	128.7[a]
C(9)	118.4	118.6	118.1	118.6
C(10)	120.2	120.6	120.1	120.7
C(11)	121.6	121.8	121.8	122.5
C(12)	110.3	111.6	112.3	109.8
C(13)	134.1	134.8	133.9	133.1[a]
C(14)	81.9	86.3	128.0	124.2
C(15)	44.4	66.9	128.2	126.3
C(16)	35.0	40.6	37.6	43.2
C(17)	25.1	23.8	28.5	31.0
C(18)	20.8	20.8	20.2	20.8
C(19)	44.5	44.5	44.8	44.9
C(20)	28.9	24.5	27.2	24.9
C(21)	7.6	6.5	8.6	9.4
C=O	174.4	172.5	163.8	163.5
OMe	54.4	53.8	52.4	53.3

[a] Assignments confirmed via selective $^{13}C\{^1H\}$ measurements by irradiating H-3, H-9 and H-12, respectively.

interpretation of these ^{13}C shift differences between **1** and **2** as being indicative of the α position of the C(15)-Cl in **2** is justifiable only upon assuming that the rotameric population distribution about the C(16)-C(20) bond of the C(16)-Et group is not perturbed significantly when going from **1** to **2**. (This issue will be taken up in more detail below). The one point where our NMR investigations fell short of giving unambiguous information was the determination of the configuration of C(14) in **2**, wherefore an X-ray study of **2** was undertaken (see below).

Several chemical shift differences in Tables 1 and 2 stand out as being worth reflecting on. In **4**, as a result of the introduction of the Cl atom, C(20), C(3) and C(17) are shifted -2.3, -2.6 and +2.5 ppm, respectively, from their values in **3**. While the effect on C(20) clearly stems from the Cl ↔ C(20)H_2 γ-interaction, the shifts on C(17) and C(3) are somewhat

Table 3. Some of the ^1H-^1H NOE Connectivities for Compounds 1 - 4.

Compound	*irr. H.*	*Observed Enhancement* H_x-20	H_y-20	H_3-21	H_c-17	H-3	other
1[c]	H-3	3.5%	0.7%	1.4%	-	*	H_α-15(3.7%);H_a-5(4.6%)
	H_3-21	3.2%[a]	2.8%[b]	*	3.2%[a]	1%	H_β-15(1.6%);H_α-15(2.8%)[b]
2	H-3	5.9%	~1%	-	-	*	H_a-5(4.6%)
	H_3-21	2.7%	2.4%	*	2.0%	-	H-15(4.6%)
	H-15	-	-	5.4%	2.5%	-	OH(4.1%)
3	H-3	3.8%[a]	3.8%[a]	3.7%	-	*	H_a-5(4.3%)
	H_3-21 ($\rightarrow$Ha-17)	3.9%[b]	3.9%[b]	*	5.1%	2.4%	H-15(3.4%)
4	H-3	1.8%	-	9.3%	-	*	H_a-5(4.6%)
	H_3-21	5.0%	5.0%	*	-	5.8%	

[a,b] For each compound like superscripts depict overlapping signals that both contribute to the measured enhancement. [c] For **5** analogous enhancements were of the same intensity as for **1** within experimental error.

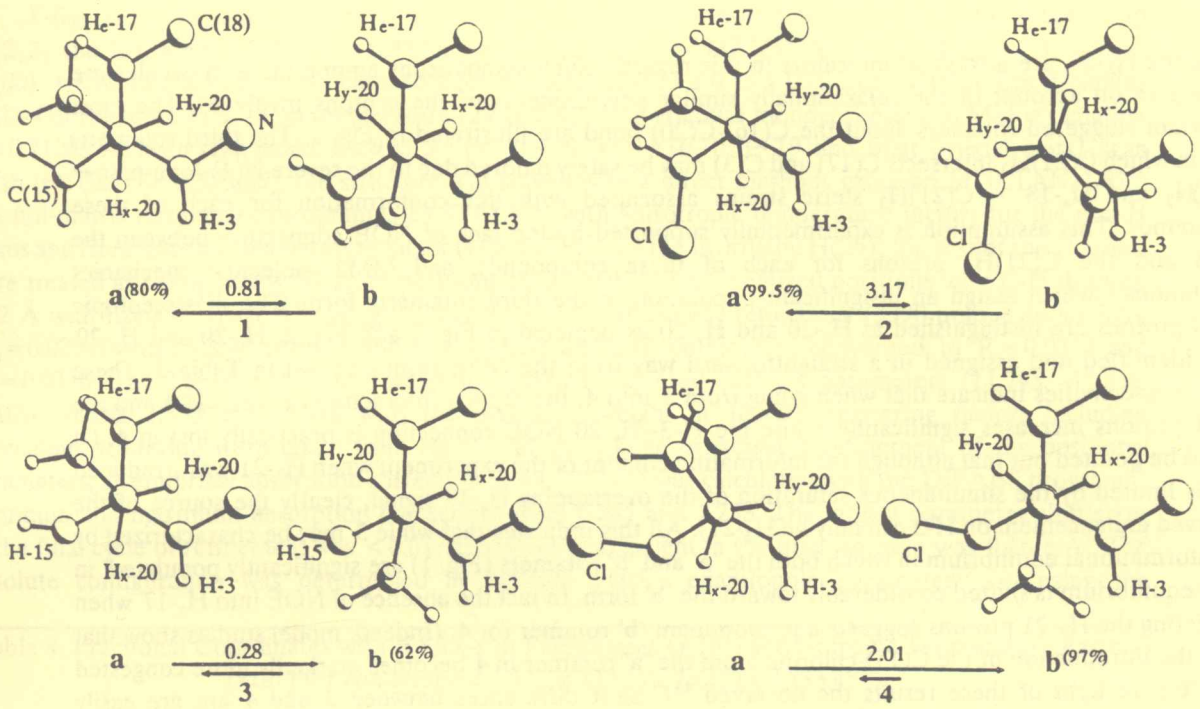

Fig 1. MM2 energy-minimized representations, as generated by the PLUTO program, of the two most likely staggered rotamers of the C(16)-ethyl group in compounds **1**-**4**. The calculated energy differences (in kcal/mole above the arrows) between the two rotameric forms, together with the approximate percentages of the main conformations at 24°C, are also shown.

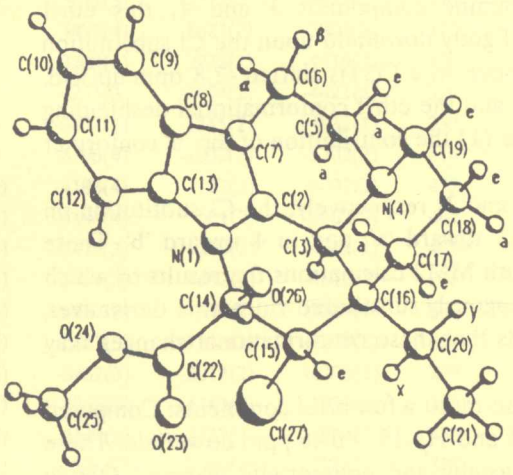

Fig 2. An X-ray determined perspective view of compound **2** showing the atomic labelling.

inconsistent with those expected from the γ-shift increments for Cl[10]. Therefore, with reference to the remarks made on the C(20)-Et group above, we attribute these shift differences between **4** and **3** as being at least partly due to a substantial difference in the conformational equilibrium about the C(16)-C(20) bond. Indeed, this observation prompted us to take a closer look at this aspect of the structures of compounds **1** - **4** by evaluating the relevant NOE contacts (Table 3) in these molecules.

In general, the intensity of the H-3--H_3-21 NOE connection provides the most sensitive and reliable information on the conformational characteristics of the C(16)-Et group. In addition, the enhancements observed on the H_2-20 protons upon irradiating H-3, together with those measured on H_e-17 upon

saturating H_3-21, are also good indicators in this regard. (Such comparisons among these molecules are reasonable on account of the relaxationally similar environments of the protons involved). The most important staggered rotamers about the C(16)-C(20) bond are illustrated in Fig. 1. The third rotameric form in which $C(21)H_3$ intersects C(17) and C(3) may be safely ignored due to the severe N(4)-lone-pair ↔ $C(21)H_3$ and H_a-18 ↔ $C(21)H_3$ steric strains associated with this conformation for each of these compounds. This assumption is experimentally supported by the lack of NOE connection between the H_a-18 and the $C(21)H_3$ protons for each of these compounds, and MM2 molecular mechanics calculations[11] which assign an insignificant population to the third rotameric form. The diastereotopic H_2-20 protons are distinguished as H_x-20 and H_y-20 as depicted in Fig. 1 and Fig. 2. H_x-20 and H_y-20 were identified and assigned in a straightforward way from the NOE results shown in Table 3. These NOE connectivities indicate that when going from **3** into **4**, the dipolar interaction between H-3 and the H_3-21 protons increases significantly, while the H-3--H_y-20 NOE connection is practically lost in **4**. (It should be pointed out that although the information content of the experiment when H_3-21 was irradiated in **3** is limited by the simultaneous saturation of the overlapping H_a-17 signal, clearly the source of the observed enhancement on H-3 can only be H_3-21). All this indicates that while **3** may be characterized by a conformational equilibrium in which both the '**a**' and '**b**' rotamers (Fig. 1) are significantly populated, in **4** the equilibrium is shifted considerably toward the '**b**' form. In fact the absence of NOE into H_e-17 when irradiating the H_3-21 protons suggests a predominant '**b**' rotamer for **4**. (Indeed, model studies show that upon the introduction of the C(15)-chlorine atom the '**a**' rotamer in **4** becomes markedly more congested than '**b**'). In light of these results the observed ^{13}C shift differences between **3** and **4** are are easily understood: The C(17) ↔ $C(21)H_3$ γ_{gauche} interaction that is associated with the contribution of the '**a**' rotamer in **3** is absent in **4**, and C(17) is therefore shifted downfield (+2.5 ppm) in **4**. On the other hand, for the same reason C(3) becomes sterically more compressed in **4**, which explains the upfield shift of -2.6 ppm on this carbon.

In the case of vincamine (**1**) the NOE results reflect the presence of an '**a**'⇔'**b**' equilibrium in which both rotamers contribute, but '**a**' is clearly preferred (cf. NOE data on **3**). On the other hand **2** possesses a virtually homogeneous '**a**' conformation, as indicated by the vanishing of the H_3-21--H-3 NOE contact and the simultaneous increase of the H-3--H_x-20 dipolar interaction. Clearly, this shift toward the '**a**' rotamer is the result of the Cl ↔ $C(21)H_3$ steric compression in the '**b**' form of the chloro compound **2** (Fig. 1). Following a similar argument as for the apovincamine compounds **3** and **4**, this ethyl conformational effect alone would be expected to move C(3) slightly downfield upon the Cl substitution of H_α-15 in vincamine (**1** → **2**). However, as was pointed out above, in **2** C(3) is shifted -2.8 ppm upfield, which is probably a result of the combined Cl γ_{gauche} shielding and the ethyl conformational deshielding effect. This upfield shift of C(3) also suggests that in vincamine (**1**) the contribution of the '**a**' conformer is relatively minor.

In conclusion, relative to the two "parent" compounds **1** and **3**, respectively, the Cl subtitution on C(15) shifts the '**a**'⇔'**b**' equilibrium in the opposite sense: in **2** toward '**a**', and in **4** toward '**b**'. These conclusions were also verified, and were in good agreement, with MM2 calculations the results of which are depicted in Fig. 1. During the structural elucidation of analogously substituted vincamine derivatives, one must therefore be careful not to ignore the possible effects that these conformational changes may bring about on the relevant ^1H and ^{13}C chemical shifts.

Some further shift differences among these compounds also merit a few brief comments: Compared to **1**, in 14-epivincamine (**5**) H_α-15 is shifted -0.24 ppm upfield and $H\beta$-15 +0.46 ppm downfield. These shifts are in good agreement with the shift increments for axially and equatorially oriented OH in cyclohexane derivatives[12]. It is further noted that in the apovincamine compounds (**3**, **4**) H_a-17 moves significantly upfield from its value in **1** and **2**. Clearly, this is partly due to the loss of the OH ↔ H_a-17 van der Waals interaction present in **1** and **2** (Fig. 2), and partly to the anisotropic shielding effect of the C(14) = C(15) bond. The former contribution may be demonstrated by the similar loss of the OH ↔ H_a-17 interaction in the 14-epi compound **5**, where H_a-17 also shows an upfield shift relative to **1**.

X-Ray structure determination of **2**. The crystals of **2** are orthorhombic (M_w = 388.90), space group $P2_12_12_1$ (no.19), a = 8.516(2), b = 4.029(1), c = 6.215(2) Å, V = 1937.3(5) Å^{-3}, Z = 4, D_{calc} = 1.33 g/cm^3, *F(000)* = 824. Intensities were measured from a crystal of 0.23 x 0.15 x 0.20 mm^3 with an Enraf-Nonius CAD-4 diffractometer at room temperature (296±1 K) using graphite monochromatized MoKα radiation (λ = 0.71069 Å) $\omega/s\theta$ scan mode, $2<\theta<25°$ (h: 0→10, k: 0→16, l: 0→19 and their Friedel pairs), scan width (θ): (0.51 + 0.35tanθ). the structure was solved with a direct methods program MULTAN11/82[13] and full-matrix refinement (program CRYSTALS[14]) with anisotropic temperature factors for the non-H atoms and fixed isotropic temperature factor (U = 0.07 Å^2) for the hydroxilic H(25); the rest of the H atoms were treated as riding atoms (H-atom positions calculated to their idealized positions with C-H distance 1.02 Å with fixed U = 0.07 Å^2) using 2480 (Friedel pairs included) reflections (3390 unique reflections, R_{int} = 0.0204) with I > 3σI (from counting statistics) and 248 parameters converged to R = 0.0322 and R_w = 0.0316. The Tukey and Prince weighting scheme was used with six parameters (11.795, -17.816, 14.076, -6.630, 3.038 and -0.448 with the maximum weight of 10000). Scattering factors including anomalous scattering were taken from ref. 15. In the course of isotropic refinement of the positional parameters, an empirical absorption correction (μ = 0.22cm^{-1}) was calculated with the DIFABS program[16]; minimum and maximum absorption corrections were 0.845 and 1.238. The largest parameter shift/error in the final cycle of refinement was < 0.01; maximum peak height in the final $\Delta\rho$ map was 0.26 e/Å^3. The absolute configuration was determined by refining Flack's enantiopole parameter[17], *x*, using the

Table 4. Fractional Coordinates with E.S.D.-s in Parentheses (x 10^4) and Isotropic Temperature Factors (x10^5) for compound **2** {U_{iso} = [U(11) x U(22) x U(33)]$^{1/3}$}.

Atom	x/a	y/b	z/c	U_{iso}(Å^2)	Atom	x/a	y/b	z/c	U_{iso}(Å^2)
Cl(27)	-8600.4(7)	-1965.7(5)	-2584.8(4)	461	C(25)	-10417(4)	-85(3)	-4141(2)	713
O(23)	-8795(2)	416(1)	-2820(1)	515	H(25)	-3914(37)	-4334(21)	-2369(21)	700
O(24)	-8844(2)	-429(1)	-3978(1)	490	H(1)	-6082	-3041	-3074	700
O(26)	-5574(2)	154(1)	-2832(1)	354	H(2)	-4410	-4057	-3949	700
N(1)	-5871(2)	-1046(1)	-3788(1)	297	H(3)	-2492	-4016	-3751	700
N(4)	-3720(2)	-3161(1)	-2989(1)	313	H(4)	-3494	-3252	-5056	700
C(2)	-5109(3)	-1919(2)	-3738(1)	279	H(5)	-2058	-2722	-4530	700
C(3)	-5171(3)	-2575(2)	-3011(1)	276	H(6)	-3110	-1462	-6030	700
C(5)	-3492(4)	-3621(2)	-3805(1)	375	H(7)	-3804	49	-6610	700
C(6)	-3209(4)	-2923(2)	-4515(2)	426	H(8)	-5335	1158	-5853	700
C(7)	-4231(3)	-2074(2)	-4421(1)	329	H(9)	-6497	739	-4537	700
C(8)	-4403(3)	-1245(2)	-4932(1)	330	H(10)	-6744	-882	-1871	700
C(9)	-3796(4)	-1002(2)	-5702(2)	416	H(11)	-4093	-1147	-1408	700
C(10)	-4183(4)	-127(2)	-6033(2)	472	H(12)	-3762	-954	-2406	700
C(11)	-5144(4)	501(2)	-5602(2)	467	H(13)	-2746	-2641	-1496	700
C(12)	-5774(3)	280(2)	-4843(2)	405	H(14)	-1574	-1749	-1780	700
C(13)	-5407(3)	-612(2)	-4518(1)	316	H(15)	-2091	-2102	-3206	700
C(14)	-6587(3)	-577(2)	-3087(1)	306	H(16)	-1402	-3060	-2718	700
C(15)	-6821(3)	-1310(2)	-2378(2)	319	H(17)	-5039	-3208	-1469	700
C(16)	-5462(3)	-2014(2)	-2203(1)	299	H(18)	-6927	-3041	-1697	700
C(17)	-3963(3)	-1464(2)	-1970(2)	383	H(19)	-6506	-2824	-266	700
C(18)	-2548(3)	-2133(2)	-1934(2)	456	H(20)	-5202	-1969	-462	700
C(19)	-2325(3)	-2599(2)	-2764(2)	373	H(21)	-7089	-1803	-690	700
C(20)	-5916(3)	-2715(2)	-1513(2)	428	H(22)	-10840	-356	-4680	700
C(21)	-6204(5)	-2292(3)	-664(2)	637	H(23)	-11152	-264	-3669	700
C(22)	-8203(3)	-140(2)	-3285(2)	368	H(24)	-10347	640	-4184	700

CRYSTALS program and a value of -0.02(7) was obtained indicating the correct enantiomer. The molecular geometry obtained corresponds with the known (+)-vincamine. Positional parameters with e.s.d.'s and equivalent isotropic temperature factors are given in Table 4. A view of the molecule (program PLUTO[18]) with the labelling scheme is presented in Fig. 2.

EXPERIMENTAL

Mp-s are uncorrected. Optical rotations were recorded in chloroform or methanol at 25 ± 2 °C. IR spectra were taken on a Specord IR 75 spectrometer using KBr pellets. Mass spectra were run on an AEI-MS-902 (70 eV; direct insertion) mass spectrometer. NMR measurements were carried out on a Varian VXR-300 instrument (300 MHz for ^1H and 75 MHz for ^{13}C) at 24 °C in $CDCl_3$. Chemical shifts are given relative to $\delta_{TMS}=0.00$ ppm. The COSY (COSY-90, magnitude mode), HETCOR and NOE experiments were recorded by using the standard spectrometer software package. The HETCOR experiments were run with ^1H decoupling in the F_1 dimension. NOEs were measured in non-degassed samples with 4 s pre-irradiation times. FIDs were exponentially multiplied prior to Fourier transformation (LB = 1 Hz). For the selective $^{13}C\{^1H\}$ NOE measurements the pulse-sequence described by Sanchez-Ferrando[19] was employed, using 8 s pre-irradiation times and a 3 Hz exponential line-broadening before Fourier transformation.

Synthesis

(+)-15α-Chloro-vincamine (2.HCl and 2). A/ from **3**: To a solution of (+)-apovincamine (**3**; 6.7 g; 20 mM) in concentrated hydrochloric acid (70 ml), a solution of sodium nitrite (3.6 g; 50 mM) in water (20 ml) was added dropwise (10-15 min) at 10-15°C, and the mixture was stirred for 15-20 min., then diluted with iced water (80 ml) and the precipitate filtered off and washed with water (3 x 15 ml). The crude product was treated in hot acetone (50 ml), filtered off, washed with acetone (2 x 15 ml) and dried to give **2**.HCl (6.42 g; 75.9 %), mp 214-220 °C.

2.HCl (6.4 g) was dissolved in a mixture of methanol / water (85 ml / 20 ml), the hot solution was cleared with active carbon, filtered and the pH of the filtrate was adjusted to 8 by using concentrated aqueous ammonium hydroxide solution (5 ml). The filtrate was kept in refridgerator overnight. The obtained crystals were filtered off, washed with water (2 x 10 ml), dried to yield **2** (5.6 g; 72.3 %), mp 190-192 °C, $[\alpha]_D=+115.2°$ (c=0.2; $CHCl_3$).

IR: 3450, 1720 cm^{-1}

MS (m/e, %): 391 (8); 390 (37); 389 (32); 388 (100, M^+); 387 (25); 373 (7, M-15); 354 (26), 353 (77, M-35); 352 (43); 351 (14); 341 (5, M-47); 336 (6); 335 (13, M-53); 329 (12, M-59); 324 (6); 232 (24); 320 (6); 318 (14, M-70); 307 (9, M-81); 300 (6, M-88); 295 (7); 294 (18, M-94); 293 (16); 282 (12, M-106); 266 (16); 265 (35, M-123); 264 (21); 263 (14); 253 (24); 252 (48, M-136); 251 (20); 237 (10); 236 (7); 225 (8); 224 (40); 209 (8); 195 (5); 194 (9); 180 (13); 168 (8); 167 (8); 153 (9); 147 (7); 133 (6); 132 (10).

B/ from **1**: To a solution of (-)-vincamine (**1**; 28.3g; 80 mM) in concentrated HCl (340 ml), a solution of sodium nitrite (14 g; 0.2 M) in water (980 ml) was added dropwise (10-15 min) at 10-15 °C, and the mixture was stirred for 15-20 min. The mixture was diluted with iced water (300 ml) and the precipitate was filtered off and washed with water (3 x 50 ml). The crude product was treated in hot acetone (200 ml), filtered off, washed with acetone (2 x 50 ml) and dried to give **2**.HCl (27 g; 79.8 %).

C/ from 3 without isolation of **2**: To a solution of **3** (6.72 g; 20 mM) in concentrated HCl (70 ml), a solution of sodium nitrite (3.6 g; 52 mM) in water (20 ml) was added according to the above procedure. After 15 min. chloroform (250 ml) and broken ice (200 g) were added. The mixture was alkalized to pH 8 by adding concentrated aqueous ammonium hydroxide solution (70 ml). The organic layer was separated, the aqueous phase was extracted with chloroform (2 x 100 ml), and the combined organic phase was washed with water (3 x 100 ml) and dried (Na_2SO_4). The filtrate was evaporated *in vacuo* and the residue (5.6 g; 72.3 %) was crystallized from methanol to give **2**.

(+)-15α-Chloro-vincaminic acid ethyl ester (6). The treatment of **7** (20 g; 57 mM) according to procedure "A" [HCl (140 ml), sodium nitrite (10 g / water (40 ml))] afforded **6**.HCl (14.4 g; 57.4 %), mp 204-207 °C (from ethanol).

After basification **6**.HCl yielded **6** (12.8 g; 55 %), mp 194-196 °C, $[\alpha]_D = +101.7°$ (c =0.2; $CHCl_3$).

IR: 3440, 1715 cm^{-1}.

MS (m/e, %): 404 (35), 403 (29), 402 (100 M^+), 401 (19, M-1), 384 (1.7, M-18), 373 (9, M-29), 367 (74, M-Cl), 355 (6, M-47), 349 (17, 367-18), 337 (7), 332 (9, M-70), 329 (19, M-73), 321 (9), 293 (11), 280 (7), 265 (18), 264 (16), 263 (12), 253 (22), 252 (53), 251 (12), 237 (12), 224 (24), 223 (7), 222 (6), 209 (7), 180 (9).

^1H NMR ($CDCl_3$), δ: 0.92 (3H, t, H_3-21); 1.25 (3H, t, OCH_2CH_3); 1.37 (1H, m, H_e-18); 1.55 (1H, m, H_e-17); 1.68 (1H, m, H_a-17); 1.80 (1H, m, H_a-18); 1.84 (1H, dq, H_x-20); 2.44 (1H, m, H_a-19); 2.48 (1H, dq, H_y-20); 2.56-2.68 (2H, m, H_α-6, H_e-19); 2.99, (1H, m, H_β-6); 3.29-3.41 (2H, m, H_2-5); 4.15 (1H, s, H-3); 4.29 (1H, s, H-15); 4.29-4.45 (2H, m, OCH_2CH_3); 4.48 (1H, s, OH); 7.05 (1H, m, H-12); 7.09-7.18 (2H, m, H-10, H-11); 7.49 (1H, m, H-9).

Reaction of apovincaminic acid ethyl ester N-oxide (8) with thionyl chloride. **8** (1.08 g; 3 mM) was dissolved in benzene (30 ml) at room temp. and thionyl chloride (0.4 ml; 6 mM) was added and the mixture was stirred for 24 h. The mixture was evaporated to dryness *in vacuo* and the residue dissolved in a mixture of ethyl acetate / water (60 ml / 15 ml) and alkalized to pH 8 by adding aqueous ammonium hydroxide solution (1 ml). The organic layer was separated and washed with water (2 x 10 ml), dried (Na_2SO_4), filtered and the filtrate was evaporated in reduced pressure. The residue (0.96 g) was chromatographed on silica (30 g; eluent: chloroform, 200 ml; chloroform / methanol 9 / 1, 200 ml). The solvent was evaporated under reduced pressure and the residue was crystallized from acetone to give **6** (0.35 g; 29.6 %).

(-)-15-Chloro-apovincamine (4). A mixture containing **2** (0.77 g; 2 mM) and p-toloene sulphonic acid monohydrate (0.95 g; 5 mM) in benzene (30 ml) was refluxed using a water-separating device for 2 h and then cooled. After adding 10 ml of water, the pH was adjusted to 8 by using concentrated aqueous ammonium hydroxide solution (1 ml). After extraction the organic phase was washed with water (2 x 10 ml), dried (Na_2SO_4), filtered and the filtrate was evaporated under reduced pressure. The residue was crystallized from methanol (5 ml) to afford **4** (0.62 g; 84.9 %), mp 162-166 °C, $[\alpha]_D = -27.4°$ (c =0.2; $CHCl_3$).

IR: 3480, 1710 cm^{-1}.

Catalytic reduction of **2**. **2** (0.38 g; 1 mM) was dissolved in a mixture of methanol / triethylamine (20 ml / 2 ml) and potassium carbonate (0.5 g) and 10 % Pd/C catalyst (about 50 mg) was added and the mixture was hydrogenated according to the above procedure. After 6 h the catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in a mixture of chloroform / water (30 ml / 10 ml). After extraction the organic phase was washed with water 2 x 5 ml), dried (Na_2SO_4), filtered and the filtrate was evaporated under reduced pressure. The residue (0.3 g; 84.7 %) was crystallized from acetone to give **1**. This substance was identical in all respects examined with the natural compound.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. J. Tamás for the mass spectra. Special thanks are due to Ms. K. Welker, Ms. E. Láng and Ms. M. Melegh for technical assistance. Dr. David Watkin is thanked for supplying the latest version of the CRYSTALS program and financial support from the Finnish Academy to K. R. is gratefully acknowledged.

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SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. PART LXIX[1]. SYNTHESIS OF 15-SUBSTITUTED EBURNANE DERIVATIVES

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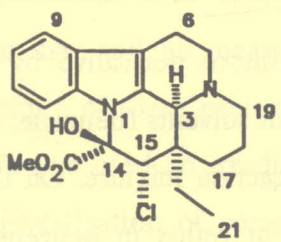
Abstract - Starting from 15α-chloro-vincamine (**1**), 15β-hydroxy 14-epi-vincamine (**2a**) and its 14-O-alkyl derivatives (**2b, 2c**) have been prepared via 14,15β-epoxy vincamine (**3**). The latter compound was transformed into (+)15-oxo-dihydroeburnamine (**6**). The structures of **2-3** were established via detailed NMR investigations.

a previous communication we described the formation of (+)-15α-chloro vincamine (**1**) from +)-apovincamine and its transformation into (+)-vincamine by reducing **1** catalitically.[2] In order to plore further reduction methods, we have treated **1** with $NaBH_4$. The reaction was carried out in ethanol, and depending on the work-up conditions of the mixture, two different compounds were tained as main products. When the reaction mixture was quenched with acetic acid in aqueous edium, 15β-hydroxy 14-epivincamine (**2a**) was isolated in 22% yield after chromatography. On the her hand, when using a large excess of methanol in the course of the acidic work-up, the -O-methyl derivative **2b** was obtained in 17 % yield.



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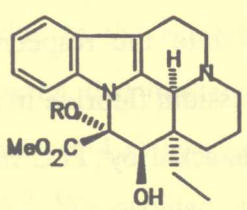
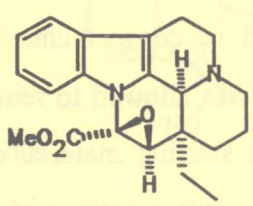


2 **a** R = H
b R = Me
c R = Et



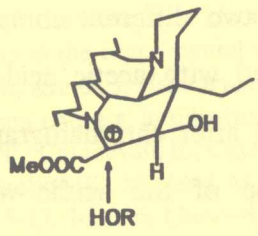
3

To rationalize the formation of these compounds, we have to assume the epoxy derivative **3** to be an intermediate. In order to verify this hypothesis, we prepared the epoxy compound by reacting **1** or its hydrochloride salt with different bases (NaOMe, NaH, KO^{t}Bu) in dry benzene. After work-up **3** was obtained as a crude product in excellent yield (91-96 %).

Compound **3** was previously prepared in low (10 %) yield, and its structure elucidated, by a French group[3].

A plausible explanation for the regio- and stereoselectivity of the cleavage of the epoxide ring is as follows: The opening of the protonated epoxy-ring gives the stabilized C-14 carbocation **4** which is favoured over the C-15 carbocation. This effect determines the position and the β orientation of the C-15 hydroxyl group. In the final step the nucleophile (H_2O or R-OH) attacks **4** from the α face. A direct attack of OR at C-14 in the protonated epoxide is of course also possible.

Starting from the epoxy derivative **3** (as a crude product), different 15-hydroxy-14-epi-vincamine derivatives were prepared. When **3** was treated with diluted sulfuric acid for 4 h at room temperature, after chromatographic work-up **2a** was isolated in 48 % yield. For obtaining the 14 β-alkoxy derivatives, **3** was treated in the appropriate alcohol in the presence of concentrated sulfuric acid at room temperature. After 4 h the desired salts (**2b**.H_2SO_4 or **2c**.H_2SO_4) were precipitated in 46-53 % yield. When the chlorohydrine **1** was reduced with $NaBH_4$ in DMSO instead of methanol, the dihydroxy compound **5** was obtained in 38 % yield. Once again, the intermediate epoxy compound **3** is likely to be attacked by the hydride anion in a similar fashion as discussed above regarding the formation of **2**. Finally, the ester group was reduced to give the alcohol **5**.



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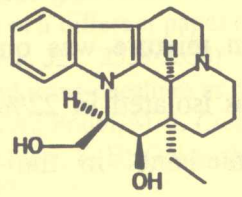

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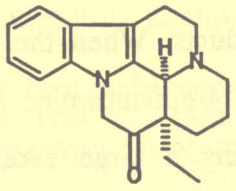


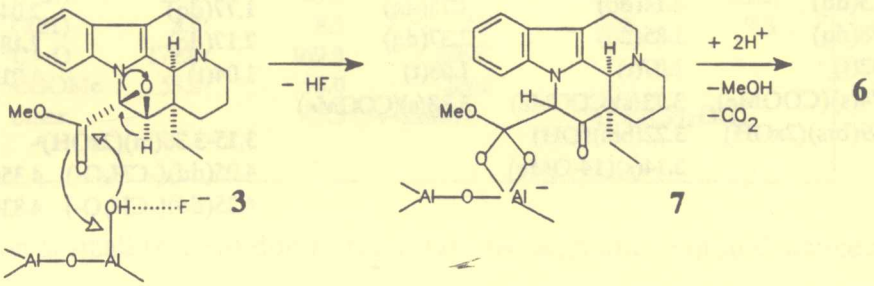
6

We also tried to convert chlorohydrine **1** into the respective 15-fluoro derivative by halogen exchange. When **1** was allowed to react with potassium fluoride in different solvents (benzene, acetone, methanol), only the starting material could be detected by TLC in the reaction mixture. On the other hand, compound **1** gave unexpected but useful reactions when heated at reflux in benzene in the presense of KF on alumina[4] (6 equivalents of reagent). After a few minutes, as monitored by TLC, **1** had already disappeared and converted into an intermediate which proved to be epoxide **3**. The reaction

mixture was heated for further 2 h. After a simple work-up (filtration, washing with water, crystallization) compound **6**[5] was obtained in 83 % yield. The presumed intermediate **3** was also allowed to react with KF on alumina, and this reaction also gave the ketone **6**. It should be noted that the alumina itself does not result in the formation of **6**, only the starting material (**1**) or epoxide (**3**) can be detected in the reaction mixture.

Epoxide **3** can react with the oxide anion of the alumina generated through deprotonation by the fluoride anion. The complex formed can probably be depicted by structure **7**. After protonation the orthoester can easily lose alcohol and CO_2. In the final step the anion formed is protonated to give the end-product **6**.

When starting from **6**, several unusual reactions have been observed which will be published elsewhere.



The structures of compounds **2**, **3**, **5** and **6** were confirmed by detailed ^1H and ^{13}C NMR studies. ^1H and ^{13}C chemical shifts are collected in Table 1 and Table 2, respectively. The assignments presented here were secured by the concerted use of 2D ^1H-^1H and ^{13}C-^1H correlation experiments and homonuclear 1D $^1H\{^1H\}$ NOE measurements. Below is a brief account of the main NMR spectroscopic features that verify the most significant stereostructural details of these compounds.

Compound **2a**. The α stereoposition of H-15 is reflected in the NOE interaction between H-15 and H-3 (ca. 6 % in both directions). (In a hypothetical C-15 epimer the long-range H-15 ↔ H-3 NOE connection may still be measurable due to the relaxationally rather isolated nature of these protons. However, that interaction should be below 1 % (we used an irradiation time of 4 s) by analogy with our previous investigation of compound **1**.[2] We avoided exploiting the γ-steric effect of the C(15)-OH group on C(17) and C(3) as potential indicators of the C(15) configuration, since the γ_{anti} and γ_{gauche} effect of the OH group can both exert significant upfield shift on the relevant carbons (cf.

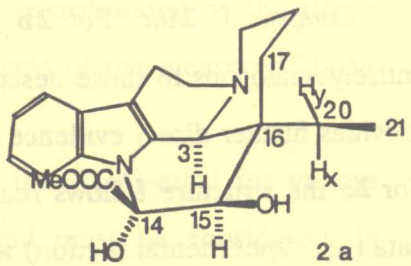


Table 1. ^{1}H Chemical Shifts for Compounds **2a, 2b, 3, 5, 6.**

Proton	**2a**	**2b**	**3**	**5**	**6**
H-3	4.02(s)[c]	4.02(s)[c]	4.04(s)[c]	3.91(s)[c]	4.40(s)[d]
H_a-5	3.21(ddd)	3.24(ddd)	3.16(ddd)	3.15-3.36(m)[a]	3.29(ddd)
H_e-5	3.33(ddd)	3.36(ddd)	3.32(ddd)	3.15-3.36(m)[a]	3.38(ddd)
$H\alpha$-6	2.52(dddd)	2.54(dddd)	2.46(dddd)	2.50-2.70(m)[b]	2.54-2.68(m)[a]
$H\beta$-6	3.00(dddd)	3.03(dddd)	2.95(dddd)	2.96(dddd)	3.06(dddd)
H-9	7.48(m)	7.48(m)	7.49(m)	7.48(m)[c]	7.55(m)
H-10	7.10-7.20(m)[c]	7.12-7.19(m)[c]	7.13-7.29(m)[c]	7.11(td)	7.13-7.25(m)[b]
H-11	7.10-7.20(m)[c]	7.12-7.19(m)[c]	7.13-7.29(m)[c]	7.17(td)	7.13-7.25(m)[b]
H-12	7.10-7.20(m)[c]	7.32(m)	7.13-7.29(m)[c]	7.48(m)[c]	7.13-7.25(m)[b]
H-15	4.25(s)	4.31(s)	3.54(s)	4.40(d)	-
H_a-17	1.36-1.45(m)[a]	1.35-1.48(m)[a]	1.01(td)	1.20(td)	1.24-1.38(m)[c]
H_e-17	1.60-1.77(m)[b]	1.35-1.48(m)[a]	1.51(ddd)	1.63(dm)	1.24-1.38(m)[c]
H_a-18	1.60-1.77(m)[b]	1.75(m)	1.66(ddddd)	1.80(ddddd)	1.86(ddddd)
H_e-18	1.36-1.45(m)[a]	1.35-1.48(m)[a]	1.43(ddddd)	1.43(ddddd)	1.46(ddddd)
H_a-19	2.57-2.66(m)[d]	2.55-2.68(m)[d]	2.48(td)	2.50-2.70(m)[b]	2.54-2.68(m)[a]
H_e-19	2.57-2.66(m)[d]	2.55-2.68(m)[d]	2.62(dm)	2.50-2.70(m)[b]	2.54-2.68(m)[a]
H_x-20	2.13(dq)	2.14(dq)	1.75(dq)	1.77(dq)	2.04(dq)
H_y-20	1.78(dq)	1.85(dq)	2.37(dq)	2.17(dq)	2.18(dq)
H_3-21	1.02(t)	1.07(t)	1.08(t)	1.04(t)	1.01(t)
other	3.74(s)(COOMe)	3.73(s)(COOMe)	3.88(s)(COOMe)		
	2.89(brs)(2xOH)	3.22(brs)(OH)		3.15-3.36(m)(2xOH)[a]	
		3.14(s)(14-OMe)		4.05(dd)(-CH_xO-)	4.35(d)($H\alpha$-14)
				4.25(dd)(-CH_yO-)	4.83(d)($H\beta$-14)

[a,b,c] Like superscripts denote overlapping signals. [d] Broadened by long-range couplings to H_2-6 (homoallylic) and H_e-17,19 ('W'). H_x-20 and H_y-20 are defined as before[2], and as depicted in the figures below.

14-epivinkamine[2]). Moreover, any C(15) substituent might alter the rotameric equilibrium about the C(16)—C(20) bond, which in turn can influence the chemical shifts of the carbons in the γ position relative to H_3-21.[2] The configuration of C(14) was indicated by the NOE connection between the $COOCH_3$ and H_{eq}-17. [This dipolar interaction is small (ca. 1 %) but clearly reproducible; a similar NOE connection can be measured in vincamine, while it is absent in 14-epivincamine].

Compound **2b,c.** For **2b** the stereostructure and the relevant NMR spectroscopic features are entirely analogous to those described for **2a.** In addition, the NOE into the 14-OMe (10%) from $H\alpha$-15 provides further direct evidence for the α position of the 14-OMe.

For **2c** the structure follows readily from a comparison of the ^{1}H data (see experimental section) with those of **2b.**

Compound **3.** The β position of the epoxy ring is indicated by the NOE found at H_x-20 (3 %) on irradiating H-15, while no NOE was measured into either H-17 proton from H-15. The H-15

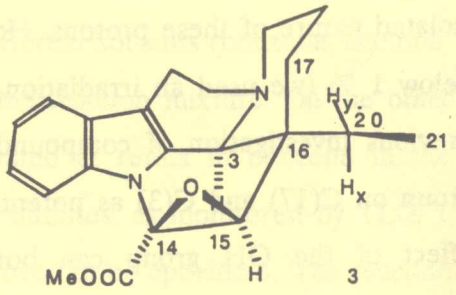
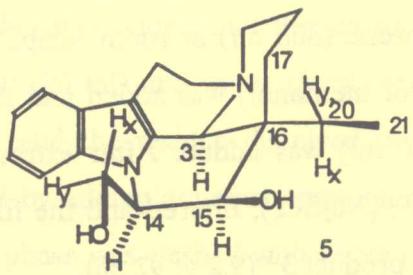


Table 2. ^{13}C Chemical Shifts for Compounds **2a**, **2b**, **3**, **5**, **6**.

	2a	**2b**	**3**	**5**	**6**
Carbon					
C(2)	131.2	131.9	130.2	130.2	129.5
C(3)	54.2	54.4	56.2	54.7	53.2
C(5)	51.2	51.2	51.4	51.5	51.5
C(6)	16.6	16.7	16.0	16.7	16.8
C(7)	106.4	107.1	107.7	104.8	105.3
C(8)	128.7	128.5	128.6	128.2	127.5
C(9)	118.4	118.0	118.5	118.2	118.5
C(10)	120.4	120.6	120.6	119.6	119.9
C(11)	121.8	122.0	121.9	120.9	121.2
C(12)	110.6	112.0	110.3	110.6	108.8
C(13)	134.5	135.6	135.8	134.7	134.8
C(14)	86.5	90.7	61.6	58.3	50.6
C(15)	81.8	73.7	63.8	72.3	206.9
C(16)	40.6	40.5	37.4	39.6	50.9
C(17)	22.7	23.0	22.9	25.4	27.9
C(18)	20.5	20.5	19.7	20.6	20.6
C(19)	45.0	45.1	44.8	45.1	43.9
C(20)	25.4	25.6	28.2	24.2	23.1
C(21)	8.4	8.3	7.8	8.2	9.3
C=O	171.8	169.0	166.5	-	
COOMe	53.8	53.0	53.4	-	
other		45.5 (14-OMe)		62.2 (CH_2OH)	

→ H-3 NOE connection is small (≈1 %) due to the relatively large interproton distance involved, and is n this case an unreliable indicator of the stereoposition of the epoxy ring.

Compound **5**. For this compound the indicated geometry, with he C(14)-CH_2-OH being dominantly in the depicted rotameric form, s secured by the following NOE connections: H-15 ↔ H-3: ≈ 5 %; H-15 → H-14: ≈ 10 %; H-14 → H-15: ≈ 5 %; OCH_x → H_{ax}-17: ≈ 5 %;OCH_y → H-12: ≈ 8 %; H-14 → H-12: ≈ 8 %.



Compound **6**. The structure follows readily from the data ollected in the tables. The C-15 position of the C=O group was further corroborated by the strong H_2-14 → H-12 NOEs. Hβ-14 and $H_α$-14 were assigned (Table 1) on the basis of the measured Hβ-14 → H_{ax}-17 NOE (2 %).

We have previously discussed the conformational characteristics of the C(16)-ethyl for various incamine analogues.[2] Two main rotamers about the C(16)—C(20) bond must be considered: In onformer 'a' H_3-21 intersects C(15) and C(17) as depicted in the figures above; in the 'b' rotamer H_3-21 intersects C(3) and C(15). For compounds **4** and **5** molecular mechanics (MM+) calculations[6] redict the following $E_{'a'}$-$E_{b'}$ = ΔE (kcal/mol) steric energy differences and corresponding $p_{'a'}$ ercentage rotameric populations calculated for 24°C: **2a-c**, **5**: ΔE ≈ +0.17($p_{'a'}$ ≈ 43 %); **3**: ΔE =

-0.445 ($p_{'a'} \approx 68$ %); **6**: $\Delta E = +0.11$ ($p_{'a'} \approx 45$ %). These population distributions are in accord with the fact that for all of these compounds H_3-21 shows NOE connections to H_{eq}-17 as well as to H-3.

EXPERIMENTAL

Mp-s are uncorrected. Optical rotations were recorded in chloroform or methanol at 25 ± 2 °C. IR spectra were taken on a Specord IR 75 spectrometer using KBr pellets. Mass spectra were run on an AEI-MS-902 (70 eV; direct insertion) mass spectrometer. NMR measurements were carried out on a Varian VXR-300 instrument (300 MHz for ^1H and 75 MHz for ^{13}C) at 24 °C in $CDCl_3$. Chemical shifts are given relative to $\delta_{TMS} = 0.00$ ppm. The COSY (COSY-90, magnitude mode), HETCOR and NOE experiments were recorded by using the standard spectrometer software package. The HETCOR experiments were run with ^1H decoupling in the F_1 dimension. NOEs were measured in non-degassed samples with 4 s pre-irradiation times. FIDs were exponentially multiplied prior to Fourier transformation (LB = 1 Hz). Molecular mechanics calculations were carried out using the MM+ facility of HyperChem™ with the default parameter-set (in vacuum, Polak-Ribiere algorythm).

Synthesis

14,15 β-Epoxy-vincamine (**3**). A/ To a solution of the hydrochloride salt of **1** (11 g; 25.8 mM) in benzene (800 ml) at room temp., sodium methoxide (prepared from 0.7 g /30 mM/ of sodium and 10 ml of methanol) was added and the mixture refluxed for 1 h. After cooling at room temp., iced water (200 ml) was added. After extraction, the organic phase was washed with iced water (3 x 100 ml), dried (Na_2SO_4), filtered and the filtrate evaporated to dryness under reduced pressure to give an oil as the product **3**[3] (9.2 g; 92 %).

B/ To a solution of **1** (0.77 g; 2 mM) in benzene (30 ml) at room temp., sodium hydride (washed with n-hexane, 0.4 g) was added and the mixture refluxed for 8 h. After cooling at room temp., the mixture was treated according to the above procedure to yield **3** (0.66 g; 95.6 %).

C/ To a solution of **1** (0.77 g; 2 mM) in dry benzene (30 ml) potassium tert.-butoxide (0.25 g; 2.22 mM) was added at room temp., and the mixture was stirred for 45 min. The mixture was treated according to the above procedure to yield **3** (0.63 g; 91.3 %).

(-)-15 β-Hydroxy-14-epivincamine (**2a**). A/ To a solution of **1** (0.77 g; 2 mM) in methanol (70 ml) sodium borohydride (0.16 g; 16 mM) was added at room temp. and the mixture was stirred for 3 h. The solvent was removed by rotary evaporation and the residue was treated with a mixture of water (30

ml) and acetic acid (30 ml). After 5 min. the pH of the mixture was adjusted to 8 by adding aqueous ammonium hydroxide solution (20 ml). the solution was extracted with ethyl acetate (3 x 20 ml) and washed with water (20 ml), dried (Na_2SO_4). The filtrate was evaporated to dryness under reduced pressure and the residue (0.6 g) was chromatographed on silica (eluent: chloroform 200 ml, chloroform/methanol 19/1 300 ml). The solvent was evaporated *in vacuo* and the residue was crystallized from ether (5 ml) to give **2a** (0.16 g; 22 %), mp 89-92 °C, $[\alpha]_D = -8.4°$ (c =0.2; $CHCl_3$).

IR: 3400, 1720, 1450 cm^{-1}.

MS (m/e, %): 370 (M^+, 93); 369 (80); 355 (6.6, M-15); 341 (8.6, M-29); 325 (12, M-45); 323 (16, M-47); 311 (28, M-59); 300 (5.1; M-70).

B/ 3 (4.4 g; oil; 12.5 mM) was dissolved in a mixture of water and concentrated sulfuric acid (100 ml/ 4 ml) at room temp. and stirred for 4 h. The mixture was basified by adding aqueous ammonium hydroxide solution (100 ml), then extracted with chloroform (3 x 50 ml). The combined organic phase was washed with water (2 x 20 ml), dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue (4.5 g) was chromatographed on silica (eluent: chloroform/methanol 19/1 500 ml; chloroform/methanol 19/1 1000 ml). The solvent was evaporated *in vacuo* and the residue was crystallized from cyclohexane (20 ml) to give **2a** (2.2 g; 47.6 %).

(+)-15β-Hydroxy-14-O-methyl-14-epi-vincamine (**2b**). A/ To a solution of **1** (0.77 g; 2 mM) in methanol (70 ml) at room temp., sodium borohydride (0.6 g; 16 mM) was added and the mixture refluxed for 4 h. After cooling at room temp., a mixture of acetic acid (20 ml) and water (5 ml) was added. After 24 h the mixture was evaporated to dryness in vacuo and the residue dissolved in a mixture of chloroform/water (40 ml/10 ml). The pH was adjusted to 8 by adding aqueous ammonium hydroxide solution (5 ml) and the phases were separated. The organic phase was washed with water (3 x 5 ml), dried (Na_2SO_4), filtered. The filtrate was evaporated under reduced pressure and the residue (0.72 g) was chromatographed on silica (eluent: chloroform 200 ml, chloroform/methanol 19/1 300 ml). The solvent was evaporated under reduced pressure and the residue was crystallized from ether (5 ml) to give **2b** (0.13 g; 17 %), mp 86-90 °C, $[\alpha]_D = +1.6°$ (c =0.2; $CHCl_3$).

IR: 3450, 1720, 1440, 1250, 1090, 1050, 710 cm^{-1}.

MS (m/e, %): 385 (22), 384 (100, M^+), 383 (88, M-1), 369 (22, M-15), 353 (2.6, M-31), 339 (1.5, M-45), 325 (14, M-59), 323 (5, M-61), 309 (3.2, M-75), 263 (4.1, M-121), 253 (15), 252 (71, M-132), 251 (16), 237 (5, M-147), 224 (4.3, M-160), 223 (5.2, M-161), 209 (3.1, M-175).

B/ 3 (4.4 g; 12.5 mM) was dissolved in a mixture of methanol/concentrated sulfuric acid (50 ml/ 1 ml) at room temp. and stirred. After 4 h the precipitated crystals were filtered off, washed with

methanol (5 ml) to give the hydrogensulfate salt of **2b** (2.78 g; 46.1 %), mp 187-192 °C, $[\alpha]_D = +37°$ (c =0.2; $CHCl_3$).

This salt (2.7 g) was dissolved in water (30 ml) and alkalized by adding aqueous ammonium hydroxide solution (3ml). The crystals were filtered off, washed with water to give **2b** (2.03 g; 42.3 %), mp 85-90 °C, $[\alpha]_D = +1.6°$ (c =0.18; $CHCl_3$).

(+)-15β-Hydroxy-14-O-ethyl-14-epi-vincamine (**2c**). Starting from **3** (2.0 g; 5.7 mM) using ethanol (30 ml) and concentrated sulfuric acid (0.7 ml), the salt of **2c** was obtained (1.5 g; 53.5 %), mp 196-198 °C, $[\alpha]_D = +1.0°$ (c =0.2; MeOH).

This salt was treated with base according to the above procedure to yield **2c** (1.0 g; 44.2 %), mp 85-89 °C, $[\alpha]_D = +1.0°$ (c =0.2; $CHCl_3$).

IR: 3450, 1720, 1440 cm^{-1}.

MS (m/e, %): 404 (35), 403 (29), 402 (100, M^+), 401 (1.7, M-1), 384 (1.7, M-18), 373 (9, M-29), 367 (74, M-Cl), 355 (6, M-47), 349 (17), 337 (7), 332 (9, M-70), 329 (19, M-73), 321 (9), 293 (11), 280 (7), 265 (18), 264 (16), 263 (12), 253 (22), 252 (53), 251 (12), 237 (12), 224 (24), 223 (7), 222(6), 209 (7), 180 (9).

^1H NMR ($CDCl_3$), δ: 1.08 (3H, t, H_3-21); 1.20 (3H, t, OCH_2CH_3); 1.30-1.53 (3H, m, H_2-17, H_e-18); 1.78 (1H, m, H_a-18); 1.85 (1H, dq, H_x-20); 2.14 (1H, dq, H_y-20); 2.55 (1H, m, H_α-6); 2.57-2.69 (2H, m, H_2-19); 3.02 (1H, m, $H\beta$-6); 3.07 (1H, dq, OCH_xCH_3); 3.26 (2H, ddd, H_a-5); 3.36 (1H, ddd, H_e-5); 3.59 (1H, dq, OCH_yCH_3); 3.70 (3H, s, OMe); 3.92 (1H, brs, OH); 4.01 (1H, s, H-3); 4.33 (1H, s, H-15); 7.12-7.17 (2H, m, H-10, H-11); 7.38 (1H, m, H-12); 7.48 (1H, m, H-9).

(-)-15b-Hydroxy-14 β-hydroxymethyl eburnamenine (**5**). To a solution of **1** (2.13 g; 5.5 mM) in dimethyl sulfoxide (30 ml) at room temperature, sodium borohydride (1.66 g; 43.8 mM) was added portionwise and the mixture was heated at 80 °C for 2 h. After cooling to room temp. the reaction mixture was poured into water (10 ml) and extracted with ethyl acetate (1 x 30, 3 x 10 ml), dried (Na_2SO_4). The filtrate was evaporated to dryness under reduced pressure and the residue (1.54 g) was chromatographed on silica (eluent: chloroform / methanol 19/1). The solvent was evaporated under reduced pressure and the residue (1.2 g; 67 %) was crystallized from ether to give **5** (0.68 g; 38 %), mp 108-111 °C, $[\alpha]_D = -57.6°$ (c =0.2; $CHCl_3$).

IR: 3284, 1457 cm^{-1}.

MS (m/e, %): 326 (M^+, 100); 325 (50); 309 (4, M-17); 307 (2.3); 297 (23, M-29); 295 (16); 279 (10); 267 (8, M-59); 256 (25, M-70); 238 (9).

(+)-15-oxo-14,15-dihydroeburnamenine (**6**). A/ To a solution of **1** (5.82 g; 15 mM) in benzene (300 ml) potassium-fluoride on alumina (92 g) was added, and the mixture was refluxed for 2 h during

intensive stirring. After cooling, the mixture was filtered off and the precipitate was washed with benzene (2 x 50 ml). The combied filtrate was washed with water (3 x 50 ml) and dried (Na_2SO_4), filtered. The filtrate was evaporated under reduced pressure and the residue (4.1 g; 95 %) was crystallized from methanol to give **6** (3.6 g; 83 %), mp 138-140 °C, $[\alpha]_D = +63.4°$ (c =1.0; $CHCl_3$).

IR: 1709 cm^{-1}.

MS (m/e, %): 294 (M+, 12); 265 (100); 224 (70); 180 (9).

B/ Starting from **1** (0.77 g; 2 mM), the epoxyde **3** was prepared as described above. The crude epoxyde 3 (0.72 g) was dissolved in benzene (30 ml) and KF on alumina (12 g) was added. The reaction mixture was treated as above. After the usual procedure compound **6** (0.49 g; 85.5) was obtained.

ACKNOWLEDGEMENTS

The authors wish to thank the late Dr. J. Tamás for the mass spectra. Special thanks are due to Ms. K. Welker for technical assistance.

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"Irgalom, édesanyám, mama, nézd, jaj kész ez a vers is!"

(József Attila)